THE SYNTHESIS OF NITROGEN RING COMPOUNDS

CONTAINING A SINGLE HETERO-ATOM [NITROGEN]

By CECIL HOLLINS, B.Sc., A.I.C.

WITH AN INTRODUCTION BY

PROFESSOR J. B. COHEN, F.R.S.



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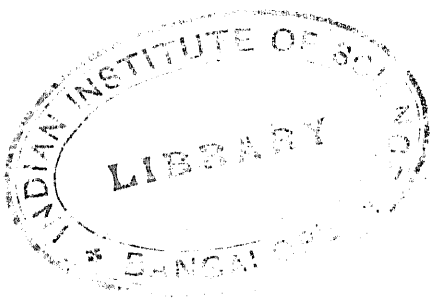
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INTRODUCTION

Specialisation in science is the natural accompaniment of increased activity in research, and this specialisation demands an ever-growing number of special treatises or monographs, which in time will, no doubt, entirely supersede the advanced text-book. Although we have been somewhat tardy in this country in adopting this form of scientific literature, we are rapidly making up for lost time.

There is no branch of organic chemistry upon which research has been so concentrated or which has assumed such far-reaching importance as that relating to the nitrogen compounds; indeed the separation of Organic Chemistry, or compounds of carbon, from what (for want of a better name) might be termed *Azotic* Chemistry, or compounds of nitrogen, might be seriously contemplated. Be that as it may, there is no doubt that a book of easy reference containing a complete list of such substances is now greatly in demand.

Mr. Hollins in the present monograph has confined himself to what is undoubtedly the more important group of ring-compounds of nitrogen, and has obviously spared no trouble in collecting and arranging this large mass of material. I have little doubt that the care he has bestowed upon it will be appreciated by a large number of chemists.

J. B. Cohen.

September 1924.

AUTHOR'S PREFACE

THIS book provides a survey of the methods by which cyclic compounds containing a single hetero-atom (nitrogen) have been prepared. It is intended to supply, within the limits indicated in the title, complete answers to the questions: What methods are available for the synthesis of a substance of a given type? and What compounds of that type have been synthesised?

The heterocyclic division has been chosen for its intrinsic interest and increasing technical importance. The further limitation to rings containing one nitrogen atom has enabled a complete survey to be made in a book of moderate size.

The book is divided into twelve chapters, in each of which the various synthetic reactions are discussed in separate sections arranged according to the type of ring-closure involved. Hydrogenated and non-hydrogenated derivatives are considered together in the same section if the methods of synthesis are of the same type. Similarly, naphtho- and benzo-derivatives are not given separate treatment unless they are prepared by fundamentally different methods. It has not been deemed necessary to distinguish between ketonic and enolic isomerides, and such compounds as isatin are written indifferently as lactams or lactims. An introductory section summarises each chapter and is intended as a guide both to the arrangement of the sections and to the selection of methods available for each type of derivative.

Yields are given wherever possible, but practical details are merely indicated, for no abstract can take the place of the original paper. Standard methods of preparation are appropriately found in laboratory text-books, but the research chemist, whether industrial or purely academic, must always obtain practical details at first hand from the original papers. The references to journals and patents are carried to December 31st, 1923.

Considerable attention has been given to the patent literature. It is well known, of course, that not all processes claimed in patents will give the results stated. On the other hand, numerous useful reactions are to be found in patent specifications which have never been the subject of communications to chemical journals. Moreover, even a patented process which fails to give the results claimed may prove exceedingly suggestive. Patent references are in most cases to German patents (D.R.-P.), since these are readily accessible in Friedländer's *Fortschritte* and Winther's *Patente der Organischen Chemie.*

The limitations of a more or less general reaction are usually as interesting and important as its applications. Unsuccessful as well as successful attempts to extend synthetic reactions have therefore been included.

The indexes will, it is hoped, be found especially useful. The subject of each Author reference is indicated by inserting the chapter number before the page number. To have included every substance mentioned in the book would have made the Subject Index too long to be useful. The *Lexicon* of Richter and Stelzner is the proper place to look for names of individual

substances, and the aim here has been rather to index the *type* of compound. Thus the pyrrole derivatives will be found under such headings as *pyrroles*, *pyrrolines*, *pyrrolidines*, *pyrrolidones*, *succinimides*, etc. Individual substances are indexed (*a*) in cases where the reaction is not general, (*b*) when they have a special interest of their own (e.g. *hydrastinine*, *atophan*, *proline*), (*c*) where their relation to the sectional heading is not immediately obvious (as, for example, in the case of the various heterocyclics obtained by Mumm from phenyl- and methyl-*iso*oxazoles).

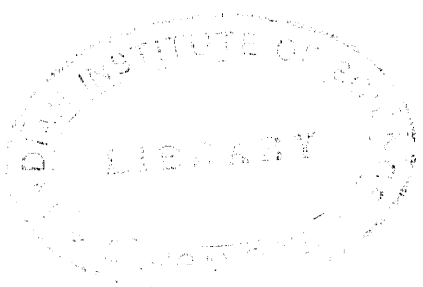
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CECIL HOLLINS.

MANCHESTER,
September, 1924.

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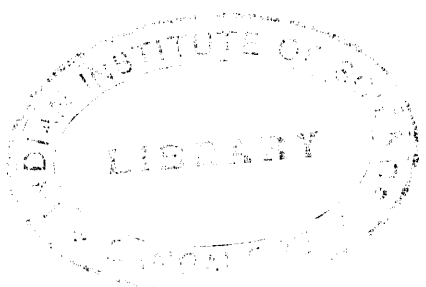
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ABBREVIATIONS EMPLOYED IN THE REFERENCES

Amer. Chem. J.	*American Chemical Journal.*
Ann.	*Annalen der Chemie* (Liebig).
Ann. Chim.	*Annales de Chimie.*
Anz. Akad. Wiss. Krakov.	*Anzeigen der Akademie der Wissenschaften zu Krakov.*
A.P.	United States Patent.
Arch. Pharm.	*Archiv der Pharmazie.*
Arch. Sci. Gen.	*Archives de Science de Genève.*
Arch. Sciences phys. nat.	*Archives des Sciences physiques et naturelles.*
Ber.	*Berichte der Deutschen Chemischen Gesselschaft.*
Ber. Deut. pharm. Ges.	*Berichte der Deutschen pharmazeutischen Gesselschaft.*
Biochem. J.	*Biochemical Journal.*
Biochem. Zeitschr.	*Biochemische Zeitschrift.*
Bull.	*Bulletin de la Société chimique de France.*
Bull. Acad. roy. Belg.	*Academie royale de Belgique—Bulletin de la Classe des Sciences.*
Bull. Mulhouse.	*Bulletin de la Société Industrielle de Mulhouse.*
Bull. Soc. chim. Belg.	*Bulletin de la Société chimique de Belgique.*
Chem. News.	*Chemical News.*
Chem. Zeitng.	*Chemiker Zeitung.*
Compt. rend.	*Comptes rendus hebdomadaires de Séances de l'Academie des Sciences.*
Compt. rend. Soc. de Chim. de Genève	*Comptes rendus hebdomadaires de la Société de Chimie de Genève.*
Dingl. polyt. J.	*Dingler's Polytechnische Journal.*
Dissn.	Dissertation.
D. Pat. Anm.	Anmeldung zu Deutsches Reichs-Patent.
D.R.-P.	Deutsches Reichs-Patent.
E.P.	English Patent.
Fr. Pat.	French Patent.
Gazz.	*Gazzetta chimica italiana.*
Helv. Chim. Acta.	*Helvetica Chimica Acta.*
J. A. C. S.	*Journal of the American Chemical Society.*
Jahresber.	*Jahresbericht für Chemie.*
J. Biol. Chem.	*Journal of Biological Chemistry.*
J. C. S.	*Journal of the Chemical Society.*
J. C. S. Abstr.	Abstracts in *Journal of the Chemical Society.*
J. Ind. Eng. Chem.	*Journal of Industrial and Engineering Chemistry.*
J. Pharm. Soc. Japan.	*Journal of the Pharmaceutical Society of Japan.*
J. pr. Chem.	*Journal für praktische Chemie.*
J. Russ. Phys. Chem. Soc.	*Journal of the Physical and Chemical Society of Russia.*
J. S. C. I.	*Journal of the Society of Chemical Industry.*
Mat. col.	*Revue générale des Matières colorantes.*
Monatsh.	*Monatshefte für Chemie.*
Nachr. K. Ges. Wiss. Göttingen.	*Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen.*
Philipp. J. Science.	*Philippine Journal of Science.*
Proc. C. S.	*Proceedings of the Chemical Society.*

Proc. Roy. Irish Academy.	*Proceedings of the Royal Irish Academy.*
Proc. Roy. Soc.	*Proceedings of the Royal Society.*
R. A. L.	*Atti della Reale Accademia Nationale dei Lincei.*
Rec. trav. chim.	*Recueil des travaux chimiques des Pays-Bas et de la Belgique.*
Sitzber. Akad. Wiss. Wien.	*Sitzungsberichte der Akademie der Wissenschaften Wien.*
Z. angew. Chem.	*Zeitschrift für angewandte Chemie.*
Zeitschr. Elektrochem.	*Zeitschrift für Elektrochemie.*
Z. Farb. Text Chem.	*Zeitschrift für Farben- und Textil-Chemie und Industrie.*
Zeitschr. physiol.	*Zeitschrift für physiologische Chemie.*
Zentr.	*Chemisches Zentralblatt.*

SYNTHESIS OF NITROGEN RING COMPOUNDS

SYNTHESIS OF NITROGEN RING COMPOUNDS

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CHAPTER I

DIMETHYLENEIMINES, $\begin{matrix}CH_2\\|\\CH_2\end{matrix}>NH$

Introductory :

COMPARATIVELY little work has been done on the preparation of three- and four-membered rings containing an atom of nitrogen :

$$\begin{matrix}C\\|\\C\end{matrix}>N \qquad \text{and} \qquad C<\begin{matrix}C\\|\\C\end{matrix}>N.$$

Dimethyleneimine is *not* obtainable by the distillation of ethylenediamine hydrochloride, as Ladenburg first supposed,[1] though this method is generally applicable to higher ring compounds. The product in this case is piperazine :

$$2NH_2\cdot CH_2\cdot CH_2\cdot NH_2 \longrightarrow NH<\begin{matrix}CH_2\cdot CH_2\\|\\CH_2\cdot CH_2\end{matrix}>NH.$$

Two general methods are available for the preparation of dimethyleneimines—Gabriel's " vinylamine " synthesis by the action of alkali upon β-aminoethyl halides, and Wolff's method by the elimination of nitrogen from triazoles and triazolines. In addition, the difficultly accessible oxalimide has been described, and de Booseré assigns a dimethyleneimine structure to the product of the action of EtMgBr upon α-chlorobutyronitrile.

The three-ring formulæ originally given to the condensation products from hippuric acid and a variety of aldehydes (also certain ketones) in the presence of acetic acid and anhydride were abandoned in favour of an oxazolone structure.[2]

$$ArCH{:}C<\begin{matrix}CO\\|\\N\cdot COPh\end{matrix} \qquad\qquad ArCH{:}C<\begin{matrix}CO-O\\|\\N=\!=CPh\end{matrix}.$$

(I.) *Old formula.* (II.) *Oxazole formula.*

Recently, however, Heller and Lauth [3] have brought forward arguments for the old three-ring structure. The compounds add on N_2H_4 in the cold, forming 2-hydrazino-oxazolidones. Now the addition of N_2H_4 at the double bond in a compound of type II is inadmissible, and Heller accordingly figures the reaction as follows :

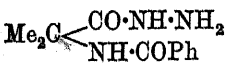
$$ArCH{:}C<\begin{matrix}CO\\|\\N\cdot COPh\end{matrix} \xrightarrow{N_2H_4} \left[ArCH{:}C<\begin{matrix}CO\\|\\N\end{matrix}\!\!-\!\!\begin{matrix}OH\\|\\CPh\cdot NH\cdot NH_2\end{matrix}\right] \longrightarrow ArCH{:}C<\begin{matrix}CO-O\\|\\NH-CPh\cdot NH\cdot NH_2\end{matrix}.$$

The same arguments are used in the case of the products obtained by Mohr [4] by the action of acetic anhydride upon the benzoyl derivatives of alanine, phenylalanine and amino*iso*butyric acid. These form hydrazino-oxazolidones by addition of N_2H_4 and are therefore formulated :

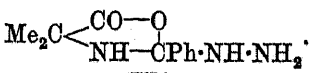
$$MeCH<\begin{matrix}CO\\|\\N\cdot COPh\end{matrix} \qquad PhCH_2\cdot CH<\begin{matrix}CO\\|\\N\cdot COPh\end{matrix} \qquad Me_2C<\begin{matrix}CO\\|\\N\cdot COPh\end{matrix}.$$

[1] Ladenburg and Abel, *Ber.*, 1888, **21**, 758.
[2] Erlenmeyer, *ibid.*, 1900, **33**, 2036; *Ann.*, 1904, **337**, 265.
[3] *Ber.*, 1919, **52**, 2300. [4] *J. pr. Chem.*, 1910, **81**, 56.

The hydrazide (III) was synthesised and found to differ completely from the N_2H_4 additive product (IV):



(III.)



(IV.)

In the absence of further evidence, however, it is convenient to consider these compounds as oxazole derivatives.

1. From aminoethyl halides: 

β-Bromoethylamine was prepared by Gabriel [1] by the phthalimide method from ethylene dibromide. It is converted by boiling water or alkali into "vinylamine" [2]:

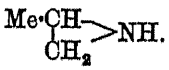
$$BrCH_2{\cdot}CH_2{\cdot}NH_2 \longrightarrow CH_2{:}CH{\cdot}NH_2.$$

The product, however, gives by the Hinsberg method a benzenesulphonamide which is insoluble in alkali.[3] It is therefore most probably a *secondary* amine* and has a cyclic structure—dimethyleneimine:

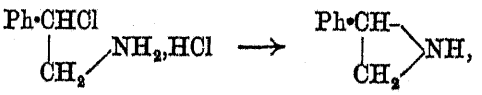


It does not decolorise $KMnO_4$, and its physical properties also are in accordance with the cyclic formula.[4]

The methyl homologue, obtained from bromopropylamine,[5] behaves in the same way, and must be regarded, not as $MeCH{:}CH{\cdot}NH_2$, but as

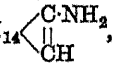


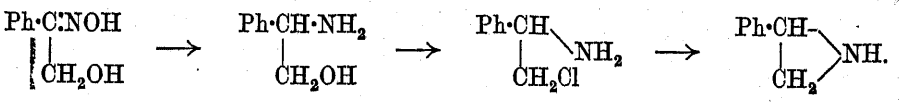
Phenyldimethyleneimine has been prepared both from β-phenyl-β-chloroethylamine,[6]



and from α-phenyl-β-chloroethylamine: [7]

[1] *Ber.*, 1888, **21**, 566, 1049. [2] Gabriel, *ibid.*, pp. 1049, 2664; Gabriel and Stelzner, *ibid.*, 1895, **28**, 2929.
[3] Howard and Marckwald, *ibid.*, 1899, **32**, 2036.
[4] Marckwald, *ibid.*, 1900, **33**, 764; 1901, **34**, 3544.
[5] Hirsch, *ibid.*, 1890, **23**, 969; Gabriel and Hirsch, *ibid.*, 1896, **29**, 2747; Böse, *ibid.*, 1920, **53**, 2000.
[6] Wolfheim, *ibid.*, 1914, **47**, 1450. [7] Gabriel and Colman, *ibid.*, 1914, **47**, 1866.

* It should be noted that camphenamine, C_8H_{14}  , also fails to give an alkali-soluble sulphonamide (Duden, *ibid.*, 1900, **33**, 477).



The identity of the products by the two methods is a satisfactory proof of their cyclic structure, for the corresponding vinylamines would be:

$$Ph{\cdot}CH{:}CH{\cdot}NH_2 \quad \text{and} \quad CH_2{:}CPh{\cdot}NH_2.$$

N-Substituted dimethyleneimines are obtained from secondary halogenated ethylamines. Thus:[1]

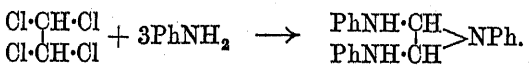


The *N*-benzyl derivative was prepared by Gabriel and Stelzner.[2]

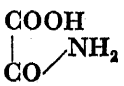
In all these cases the dimethyleneimine is accompanied by large quantities of the corresponding piperazine,

$$RN\langle \begin{matrix} CH_2{\cdot}CH_2 \\ CH_2{\cdot}CH_2 \end{matrix} \rangle NR.$$

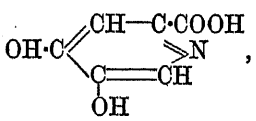
Sabanejev's base, formed in 15–20% yield by condensing tetrabromoethane or trichloroethylene with aniline,[3] has probably a dimethyleneimine structure:



Tetrabromoethylene, aniline, and KOH give the same base in 30% yield.[4] Phenyldicarbylamine (see next section) is probably an intermediate product.

2. Preparation of oxalimide: 

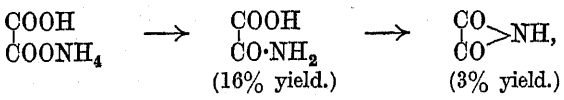
By the oxidation of comenamic acid,



with N_2O_5 in glacial acetic acid at 0°, Ost and Mente[5] obtained, amongst other products, a

[1] Knorr, Hörlein and Reith, *Ber.*, 1905, **38**, 3137. [2] *Ibid.*, 1896, **29**, 2384.
[3] Sabanejev, *Ann.*, 1875, **178**, 125. [4] *Idem, Zentr.*, 1902, ii, 121. [5] *Ber.*, 1886, **19**, 3228.

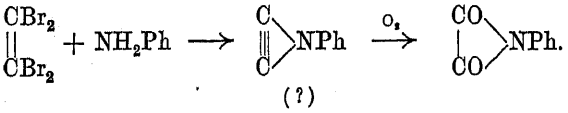
small amount of oxalimide. This was also formed in 3% yield when oxamic acid was heated at 80–90° with a mixture of PCl_5 and $POCl_3$:



(16% yield.) (3% yield.)

P_2O_5 or heat alone did not bring about the reaction.

Sabanejev,[1] by the condensation of tri- or tetra-bromoethylene with aniline in the presence of KOH and sulphur, obtained "phenyldicarbylamine," C_2NPh, which was converted by oxidation into oxanil:



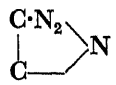
(?)

The corresponding dithio-oxanil is a product of the original reaction.

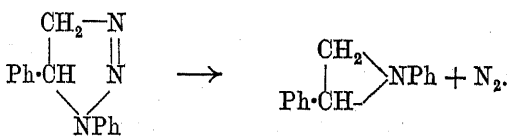
3. From α-chloronitriles and Grignard reagents: 

de Booseré[2] has recently described the formation of triethyl-dimethyleneimine by the action of two molecular proportions of ethyl magnesium bromide upon α-chlorobutyronitrile. The product might result in any of several ways, the most probable course of the reaction being:



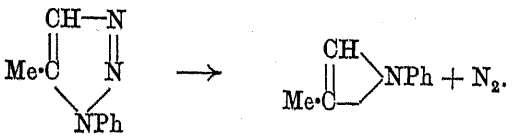
4. From triazole derivatives: 

Just as *cyclo*propanes are formed by the decomposition of pyrazolines (Buchner reaction), so Wolff[3] has obtained dimethyleneimine derivatives by heating triazolines at 130°:



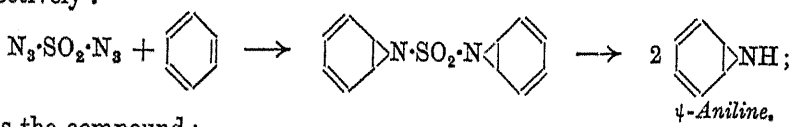
Triazoles lose nitrogen at a higher temperature:

[1] *Zentr.*, 1902, ii, 121. [2] *Bull. Soc. chim. Belg.*, 1923, **32**, 26. [3] *Ann.*, 1913, **394**, 29.



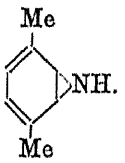
BENZODIMETHYLENEIMINES

The only examples of this type of cyclic compound are the ψ-aniline and ψ-xylidine prepared by Curtius and Schmidt[1] by the action of the diazide of sulphuric acid upon benzene and *p*-xylene respectively:



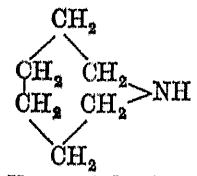
ψ-Aniline.

p-Xylene gives the compound:

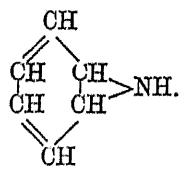


ψ-Xylidine.

An attempt to synthesise ψ-aniline by removal of hydrogen atoms from hexamethyleneimine was unsuccessful:



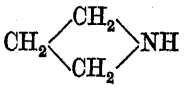
Hexamethyleneimine.



ψ-Aniline.

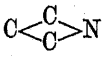
[1] *Ber.*, 1922, **55**, 1571, 1584.

CHAPTER II

TRIMETHYLENEIMINES, 

Introductory:

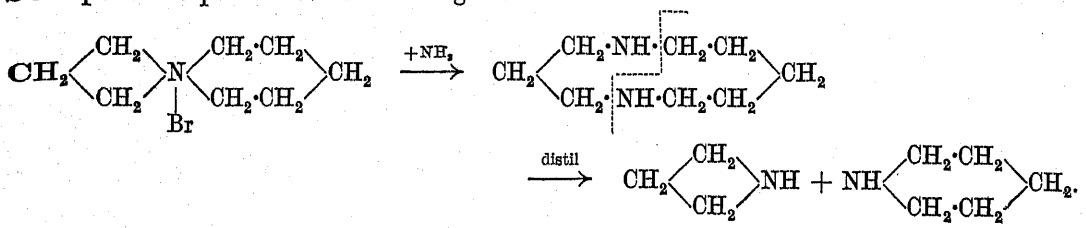
THE three general methods for the preparation of cyclic compounds of the type



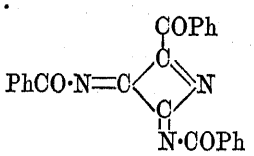
are as follows:

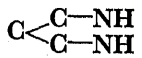
(I) Distillation of the appropriate diamine hydrochloride,
(II) Action of alkali upon γ-aminopropyl halides,
(III) Addition of ketens to *iso*cyanates or to Schiff's bases.

No attempt has so far been made to obtain trimethyleneimine from Gabriel's *spiro*-compound (p. 24) by the method successfully used by v. Braun for pyrrolidine (p. 66). The reaction might be expected to proceed in the following manner:

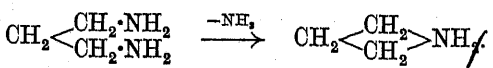


A trimethyleneimine structure has been assigned to Nef's trimeric benzoyl cyanide[1] by Diels and Stein.[2] This compound is prepared by the action of silver cyanide upon benzoyl *bromide* in ether solution (the chloride at 220° gives the ordinary monomolecular PhCO·CN), and seems to have the formula:

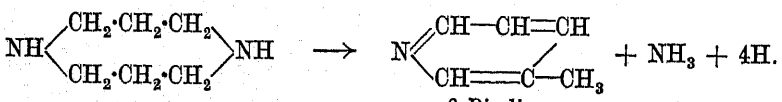


1. From trimethylenediamines: 

The distillation of trimethylenediamine hydrochloride results in the formation of a small amount of trimethyleneimine[3]:



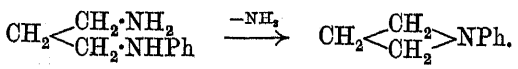
The main primary product is, however, an eight-membered ring compound which by further decomposition yields β-picoline:



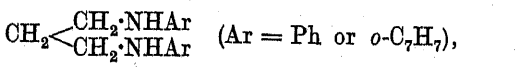
β-Picoline.

[1] *Ann.*, 1895, **287**, 303. [2] *Ber.*, 1907, **40**, 1655. [3] Ladenburg and Sieber, *ibid.*, 1890, **23**, 2727.

Balbiano [1] had previously prepared the *N*-phenyl derivative from γ-aminopropylaniline:



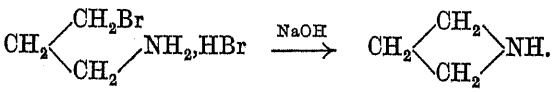
The phenyl and *o*-tolyl compounds result from the distillation of



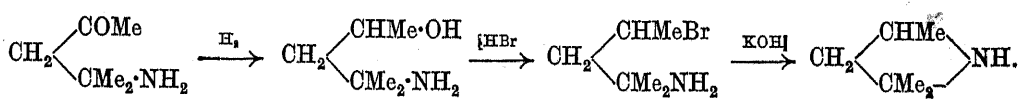
aniline and *o*-toluidine respectively being eliminated.[2]

2. From γ-aminopropyl halides: 

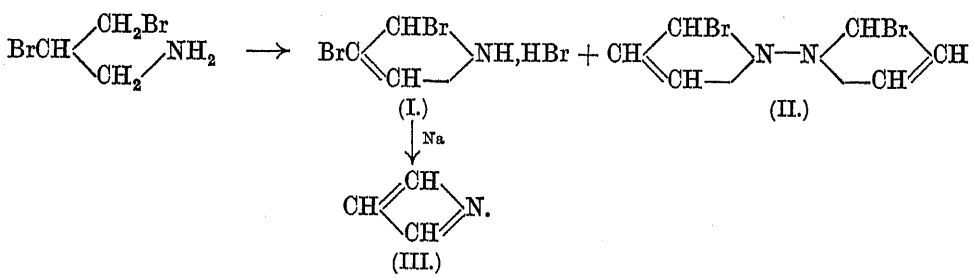
γ-Bromopropylamine hydrobromide, prepared by the phthalimide method from trimethylene dibromide, loses 2HBr when treated with alkali and forms trimethyleneimine [3]:



The 2 : 2 : 4-trimethyl derivative is prepared from diacetonamine [4]:



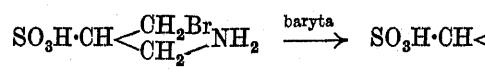
The dibromide of allylamine gives with 40% NaOH two products, I and II, the first of which is converted into the interesting compound C_3H_3N (III), when warmed with sodium [5]:



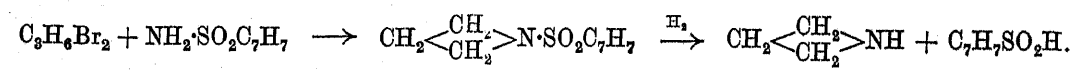
Products I and II are evidently the result of complex reactions involving the removal of Br_2 as well as HBr, and further interaction with the hypobromite so formed.

[1] *R. A. L.*, 1888, [iv], **4**, ii, 44.
[2] Scholtz, *Ber.*, 1899, **32**, 2254.
[3] Gabriel and Weiner, *ibid.*, 1888, **21**, 2675.
[4] Kahan, *ibid.*, 1897, **30**, 1318; Kohn, *Ann.*, 1907, **351**, 137.
[5] Abderhalden and Paquin, *Ber.*, 1920, **53**, 1125.

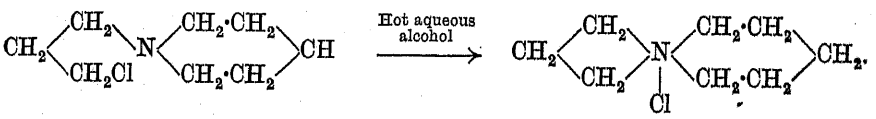
A trimethyleneiminesulphonic acid was prepared by Gabriel and Colman [1] from bromomethyltaurin :

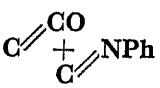


Trimethyleneimine itself is conveniently obtained by the method of Howard and Marckwald [2] from trimethylene dibromide and *p*-toluenesulphonamide, the toluenesulphonyl group being removed by reduction with sodium and amyl alcohol :

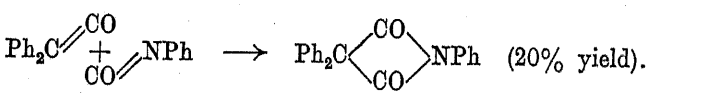


A *spiro*-derivative containing a four-membered ring was prepared by Gabriel and Stelzner [3] :



3. From ketens : 

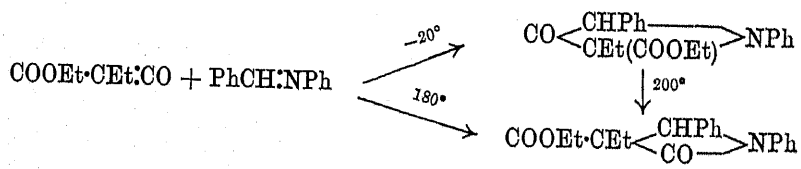
The addition of ketens to phenylcarbimide and to Schiff's bases has been investigated by Staudinger. The products are derivatives of trimethyleneimine. Thus [4] :



Formation of the isomeride



has not been observed, but in the case of Schiff's bases addition may occur in either way according to the temperature. Staudinger [5] found that ethylketencarboxylic ester combines with benzalaniline at — 20°, giving a 53% yield of a *β*-keto-imine. At 180°, the isomeric *α*-keto-imine is formed. The *β*-compound may be converted into the *α*-isomeride by heating *in vacuo* at 200° :



[1] *Ber.*, 1906, **39**, 2891.
[2] Marckwald and v. Droste-Huelshoff, *ibid.*, 1898, **31**, 3264; Howard and Marckwald, *ibid.*, 1899, **32**, 2032.
[3] *Ibid.*, 1896, **29**, 2384; see, however, Hörlein and Kneisel, *ibid.*, 1906, **39**, 1429, and the reply by Gabriel and Colman, *ibid.*, p. 2825.
[4] Staudinger, Göhring, and Schöller, *ibid.*, 1914, **47**, 46.
[5] *Ibid.*, 1917, **50**, 1035.

The α-keto-imine is evidently the more stable isomeride and is the usual product of the action of ketens upon Schiff's bases. Keten itself with benzalaniline gives only a 27% yield of additive product:

$$CH_2{:}CO + PhCH{:}NPh \xrightarrow{180-200^\circ} CH_2\!<\!\begin{matrix}CHPh\\CO\end{matrix}\!>NPh.$$

Phenylketencarboxylic methyl ester reacts similarly, forming

$$COOMe{\cdot}CPh\!<\!\begin{matrix}CHPh\\CO\end{matrix}\!>NPh.$$

Ketendicarboxylic ester, $CO{:}C(COOEt)_2$, fails to react with benzalaniline, but the dimeride of camphoketen gives at 150–160° the *spiro*-compound [1]:

$$C_8H_{14}\!<\!\begin{matrix}\\CO\end{matrix}\!>C\!<\!\begin{matrix}CHPh\\CO\end{matrix}\!>NPh.$$

Benzophenone-anil, $Ph_2C{:}NPh$, does not react so smoothly as benzalaniline. The product from ketendicarboxylic ester quickly breaks down into benzophenone and the diester-mono-anilide of methanetricarboxylic acid [2]:

$$(COOEt)_2C\!<\!\begin{matrix}Ph_2C\\CO\end{matrix}\!>NPh \longrightarrow (COOEt)_2C\!<\!\begin{matrix}CPh_2\\CO\end{matrix}\!>NPh \longrightarrow (COOEt)_2CH{\cdot}CO{\cdot}NHPh + Ph_2CO.$$

No four-membered ring compound is obtained from benzophenoneanil and phenylketencarboxylic ester, the product being a piperidine derivative (see p. 226).

4. From alkylated acetoacetic esters: $C\!<\!\begin{matrix}COOEt\\CO{\cdot}R\end{matrix}\!>+NH_3$

Although β-aminocrotonic ester shows no tendency to anhydrise, Kipping and Perkin [3] assigned a four-ring structure to the product they obtained by the action of alcoholic NH_3 upon α : ε-diacetylcapronic ester:

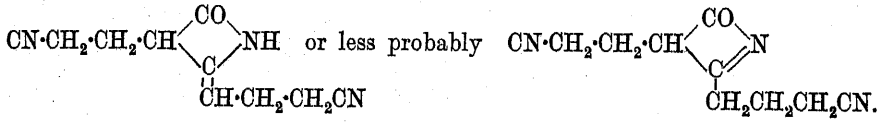
$$MeCO{\cdot}[CH_2]_4{\cdot}CH\!<\!\begin{matrix}COOEt\\COMe\end{matrix} \xrightarrow{NH_3} \left[MeCO{\cdot}[CH_2]_4{\cdot}C\!<\!\begin{matrix}COOEt\\CMe\end{matrix}\!>NH_2\right] \longrightarrow MeCO{\cdot}[CH_2]_4{\cdot}C\!<\!\begin{matrix}CO\\CMe\end{matrix}\!>NH.$$

5. From glutaric nitrile: $C\!<\!\begin{matrix}CN\\C\end{matrix}\!>NH$

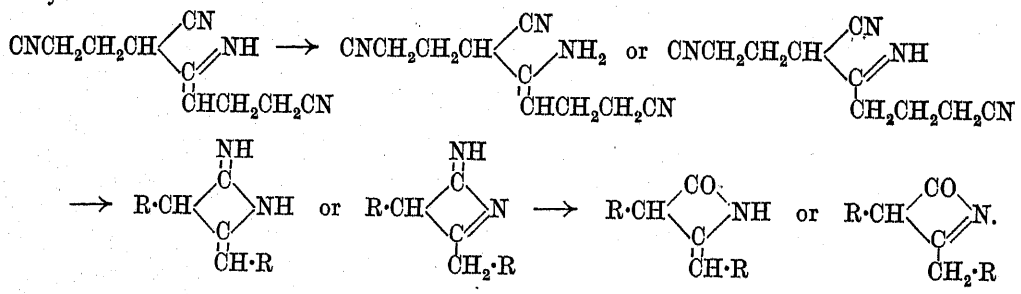
A curious reaction leading to the formation of a trimethyleneimine derivative has recently

[1] Staudinger and Schotz, *Ber.*, 1920, **53**, 1123. [2] Staudinger, *ibid.*, 1917, **50**, 1041.
[3] *J. C. S.*, 1889, **55**, 339.

been recorded by Bruylants.[1] Glutaric nitrile reacts with Grignard reagents in the form $NH{:}C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CN$, and when the product is treated with water (in the absence of acid) a compound, $C_{10}H_{11}ON_3$, is obtained, to which Bruylants assigns the structure:

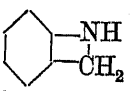


Either substance might result from the dimerisation of the regenerated nitrile, followed by hydrolysis:

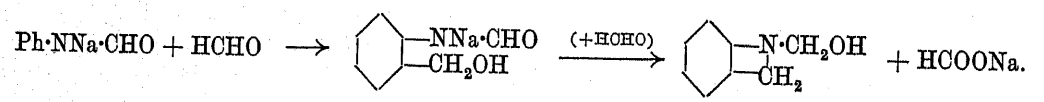


(R = $\cdot CH_2{\cdot}CH_2{\cdot}CN$.)

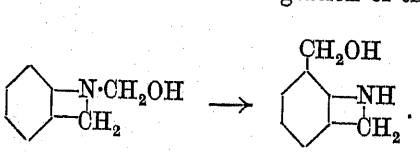
ortho-BENZYLENEIMINES

The preparation of compounds of the type  has been the subject of a number of investigations.[2] As, however, the products from *o*-, *m*- and *p*-compounds are very similar to one another, the simple ring-structure is scarcely probable, and they must be regarded as polymerides of $C_6H_4{<}^{CH_2}_{NH}$.

Interesting results were obtained by Orlov,[3] who condensed sodioformanilide with formalin and obtained a quantitative yield of *N*-methylol-*o*-benzyleneimine:



Treatment of the product with dilute acids led to migration of the methylol group to the free *ortho* position:



[1] *Zentr.*, 1921, iii, 1349.

[2] Lellman and Stickel, *Ber.*, 1885, **19**, 1611; Lellman and Pekrun, *Ann.*, 1890, **259**, 54, 58, 59; D. R.-PP. 83544, 93540, 95184, 95600, 96851; Dimroth and J. Thiele, *Ber.*, 1895, **28**, 914; E. Thiele and Weil, *ibid.*, 1650; Löb, *ibid.*, 1898, **31**, 2037; *Z. f. Elektrochem.*, 1897/8, 428; Goldschmidt, *Chem.-Zeitung*, 1900, **24**, 284; Bamberger, *Ann.*, 1912, **390**, 182.

[3] *Zentr.*, 1905, i, 674; 1906, i, 1413–1416.

Exactly similar products were prepared from other arylamines, namely: sulphanilic acid, *p*-nitroaniline, *p*-anisidine, *p*-toluidine, α- and β-naphthylamines, naphthionic acid, and 4 : 4′-diaminodiphenylmethane. Tartaric acid or citric acid may replace formic acid. In this case, the acid and formalin are first heated together in a closed vessel and the aniline is added after cooling. The product has the formula:

$$4C_6H_4\!<\!\begin{matrix}NH\\ |\\ CH_2\end{matrix}\!,3H_2O.$$

This method may be employed also with *o*-anisidine and *o*-toluidine.[1]

Acylanthranils.—Although Heller has brought weighty arguments in favour of the (benzo-)four-ring structure (I) for the acylanthranils,[2] his conclusions are not yet generally accepted. The alternative formula (II) is still preferred by many chemists, and the acylanthranils will therefore not be considered here.

$$C_6H_4\!<\!\begin{matrix}N{\cdot}COR\\ |\\ CO\end{matrix}$$

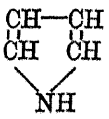
(I.)

$$C_6H_4\!<\!\begin{matrix}N{=}\!=\!CR\\ |\quad\ |\\ CO{-}\!-\!O\end{matrix}.$$

(II.)

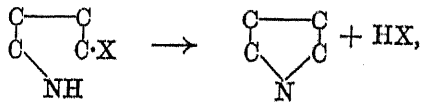
[1] See also Nastjukov and Malkaln, *Zentr.*, 1912, ii, 2070; Nastjukov and Kronenberg, *ibid.*, p. 1271.
[2] *Ber.*, 1915, **48**, 1183.

CHAPTER III

PYRROLES, 

Introductory :

THE majority of pyrrole syntheses are reactions involving ring-closure between the nitrogen atom and the *α*-carbon

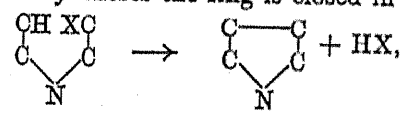


where X represents a negative group or element—usually ·OH or halogen (sections 1–12). Reactions of this type have been used for the synthesis of *pyrroles* (sects. 1, 2, 3, 9), *pyrrolines* (sects. 2, 12), *pyrrolidines* (sects. 2, 8, 10, 11, 12), *pyrrolenones* (sect. 2), *pyrrolones* (sects. 2, 4, 7, 11), *pyrrolidones* (sects. 4, 7, 8), *diketopyrrolidines* (sects. 4, 5), and *succinimides* and *maleinimides* (sect. 6). The most important are the Paal-Knorr synthesis from *γ*-diketones (sect. 1) and the similar synthesis from *γ*-aminoketones (sect. 2), both of which have been used for a large variety of pyrrole derivatives; and Willstätter's method from 1 : 4-dihalides (sect. 12).

Löffler's synthesis (sect. 13) is of similar type, the X and the H in the above scheme being interchanged. An interesting application of this method has recently been described by Ruzicka (p. 68).

Ring-closure by intramolecular addition of the NH_2 group (sects. 14, 15) leads in certain cases to *pyrrolidones*.

In a second group of pyrrole syntheses the ring is closed in the *β-γ* position :

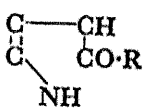


where X = ·OH or ·Cl (sects. 16–22). This type of reaction is available for the preparation of *pyrroles* (sects. 16, 17, 18), *pyrrolones* (sects. 19, 22) and *triketopyrrolidines* (sect. 21). The well-known Knorr synthesis (sect. 16) and its modifications belong to this group.

The Piloty-Robinson method (sect. 23), in which ring-closure is brought about by removal of two hydrogen atoms, is a special case of this type of synthesis.

Closure of the pyrrole ring in the *αβ*-position (sects. 24, 25, 26) occurs in only a few cases and has led to no important general method. The products may be *pyrroles* (sect. 26), *pyrrolones* (sect. 25), *diketopyrrolines* (sect. 24) or *diketopyrrolidines* (sect. 25).

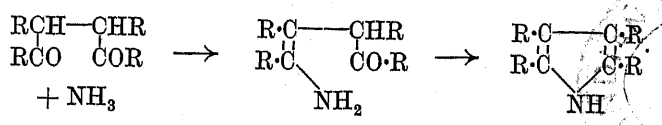
A few methods of a miscellaneous type are described in sections 27–32, including a curious *pyrrole* synthesis by addition (sect. 27), the conversion of pyridazines and pyridines into *pyrroles* and *pyrrolidines* (sects. 30, 31), and finally certain pyrogenous methods by which *pyrrole* has been obtained (sect. 32).

1. From *γ*-diketones and ammonia or amines : 

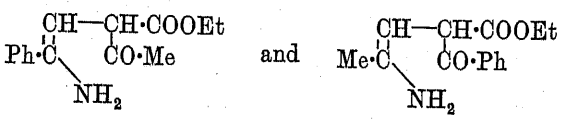
The Paal-Knorr synthesis of pyrroles from *γ*-diketones and ammonia or primary amines[1] has been found to have a very general application. Any 1 : 4-diketone capable of forming a

[1] Knorr, *Ber.*, 1885, **18**, 302; *Ann.*, 1886, **236**, 290; Paal, *Ber.*, 1885, **18**, 367, 2251.

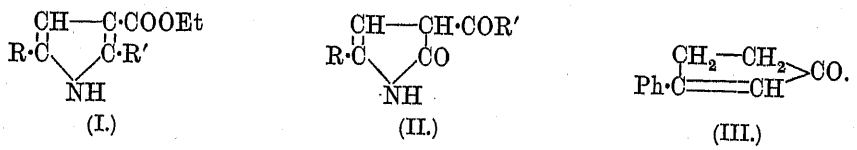
di-enol may be used with ammonia, though not all primary amines are suitable. The intermediate γ-aminoketone may in some cases be isolated by performing the reaction in dry ether at 0°:[1]



Borsche and Fels[2] isolated the intermediates

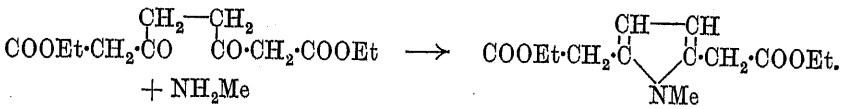


and showed that, according to the conditions, these could be converted into pyrroles (I), pyrrolones (II) or *cyclo*pentenones (III):

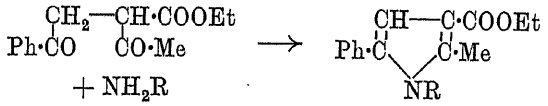


Pyrrole itself was obtained by Harries[3] by the action of ammonia upon a solution of succindialdehyde in ether and alcohol. The dialdehyde is prepared from pyrrole by treatment with NH_2OH, followed by hydrolysis of the dioxime so formed.

Primary amines usually react as easily as ammonia. Thus in Willstätter and Pfannenstiel's synthesis of ecgonin[4] the first step was the preparation of 1-methylpyrrole-2 : 5-diacetic ester from methylamine and succinyldiacetic ester:



Phenacylacetoacetic ester has been condensed with a variety of amines by Lederer and Paal[5]:



(R = H, Me, C_3H_5, Ph, *o*- and *p*-C_7H_7, α- and β-$C_{10}H_7$.)

Of the three nitroanilines[6] the best yields are given by the *meta* (70%) and *para* (56%) compounds, only little pyrrole derivative being obtained from the *ortho* compound. Acid amides do not appear to react in the desired direction, and sulphanilic acid also fails.[7]

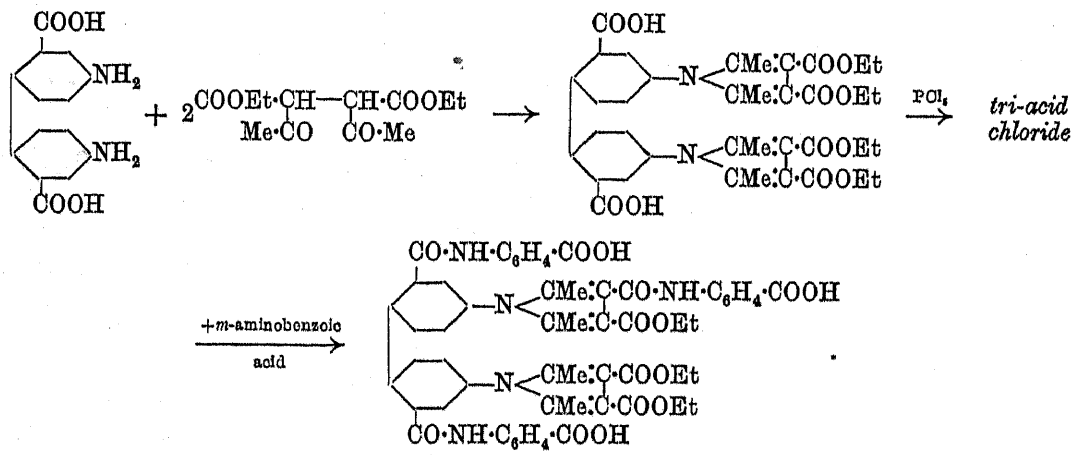
The corresponding phenacylbenzoylacetic ester is unsuitable for condensation with aliphatic

[1] Knorr and Rabe, *Ber.*, 1902, **35**, 3801; Borsche, *ibid.*, 1906, **39**, 1922, 3877.
[2] *Ibid.*, p. 3877. [3] *Ibid.*, 1901, **34**, 1496.
[4] *Ann.*, 1921, **422**, 14; D.R.-PP. 344031, 345759, 346890. [5] *Ber.*, 1885, **18**, 2591.
[6] Borsche and Titsingh, *ibid.*, 1907, **40**, 5011. [7] Paal, *Dissn. Würzburg*, 1890, p. 164.

611
547.593
N24

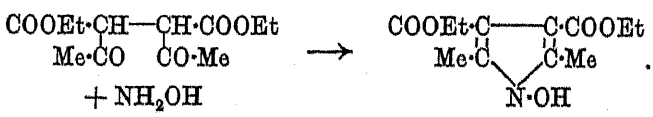
amines, no pyrrole being obtained with ethylamine, allylamine, ethylenediamine or glycine. Aromatic amines, on the other hand, give good results [1] with the exception of *m*-aminobenzoic acid.

Schmidt and Schall,[2] starting from amino- and diamino-diphenic acids, have prepared pyrrole derivatives of very high molecular weight:

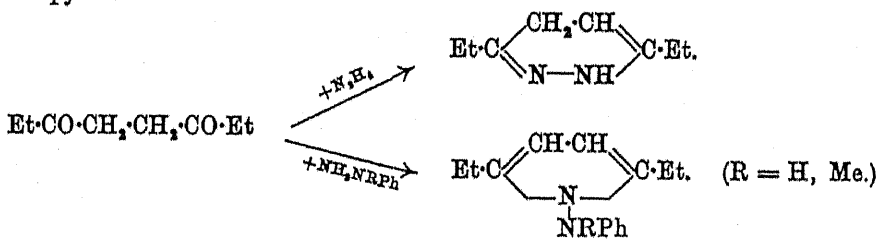


This product has a molecular weight of 1048, approaching that of Fischer's octadecapeptide (1213).

Hydroxylamine reacts with γ-diketones in the same way as ammonia, the products being *N*-hydroxypyrroles [3]:



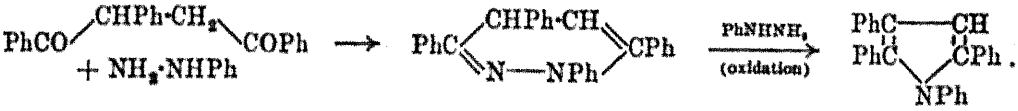
With hydrazine the reaction becomes more complex, since there may be formed, in addition to *N*-aminopyrroles, pyridazines and in some cases pyrazolones. Blaise [4] found that dipropionylethane gives with hydrazine a pyridazine, but with phenylhydrazine and phenylmethylhydrazine the *N*-aminopyrroles:



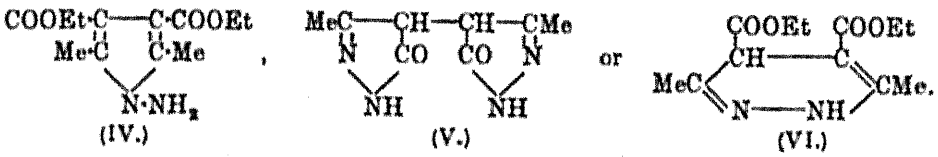
Smith [5] prepared pyridazines by the action of phenylhydrazine upon diketones of the type

[1] Paal and Braikoff, *Ber.*, 1889, **22**, 3086.
[2] *Ibid.*, 1907, **40**, 3002.
[3] Knorr, *Ann.*, 1886, **236**, 296; *Ber.*, 1885, **18**, 1569.
[4] *Compt. rend.*, 1920, **170**, 1324; **171**, 34.
[5] *J. C. S.*, 1890, **57**, 647; *Ann.*, 1896, **289**, 316.

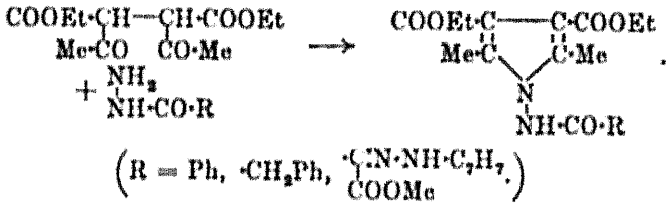
ArCO·CHAr·CH_2·COPh, where Ar represents phenyl, cumyl or piperonyl. With excess of phenylhydrazine, he obtained tetraphenylpyrrole from desylacetophenone (Ar = Ph):



The action of hydrazine upon diacetylsuccinic ester [1] may give three products according to the conditions of the experiment:



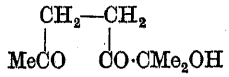
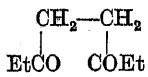
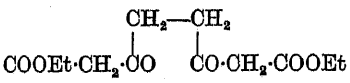
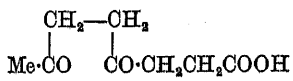
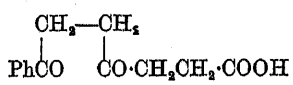
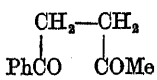
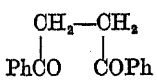
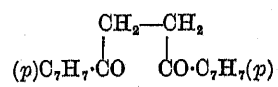
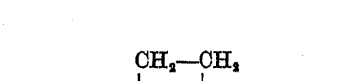
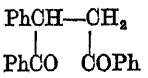
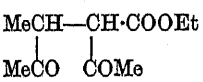
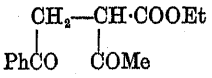
Paal and Ubber [2] obtained the dihydropyridazine (VI) as main product in alcoholic solution. The aminopyrrole (IV) was isolated by Bülow,[3] who used acetic acid as solvent. Dibenzoylsuccinic ester similarly gives with $PhNH·NH_2$ in acetic acid the aminopyrrole, but in alcohol the *bis*pyrazolone.[4] Diacetylsuccinic ester gives aminopyrroles when condensed with acid hydrazides [5]:



The following γ-diketones have been converted into pyrroles by condensation with ammonia or primary amines:

Diketone.	*Amine.*	*References.*
CH_2—CH_2 CHO CHO	Ammonia.	26
CH_2—CH_2 MeCO COMe	Ammonia.	5
	n-Amylamine.	43
	Ethylenediamine.	10
	Trimethylenediamine.	10
	Benzidine.	10
	4-Aminodiphenic acid.	35
	4 : 4′-Diaminodiphenic acid.	35
	Phenylhydrazine.	16
	N-Aminotetrazole.	34
CH_2—CH_2 MeCO CO·$CHMe_2$	Ammonia.	22

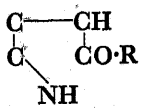
[1] Curtius, *J. pr. Chem.*, 1894, **50**, 508; Bülow, *Ber.*, 1902, **35**, 4311.
[2] *Ibid.*, 1903, **36**, 497.
[3] *Loc. cit.*
[4] Knorr and Schmidt, *Ann.*, 1896, **293**, 109.
[5] Bülow, *Ber.*, 1902, **35**, 4317; Bülow and Weidlich, *ibid.*, 1907, **40**, 4329.

Diketone.	*Amine.*	*References.*
	Ammonia.	28
	Ammonia. Phenylhydrazine. Phenylmethylhydrazine	40
	Ammonia. Methylamine.	42 41
	Ammonia.	29
	Ammonia.	25
	Ammonia.	2
	Ammonia.	12
	Ammonia.	13
	Ammonia. Methylamine. Ethylamine. Aniline. *p*-Toluidine. Phenylhydrazine. Methylphenylhydrazine. Benzylphenylhydrazine.	9 11 11 11 11 31 31 31
	Ammonia. Aniline.	15, 17, 19 19
	Ammonia. Hydrazine.	30 30
	Ammonia. Methylamine. Allylamine. Ethylenediamine. Glycine. Aniline. *o*- and *p*-Toluidines. α- and β-Naphthylamines. *o*-, *m*- and *p*-Nitroanilines *m*-Phenylenediamine. *m*-Aminobenzoic acid. Aminoazobenzene. Benzidine.	6, 33 6 6 10 10 6 6 6 37 10 10 10 10

Diketone.	*Amine.*	*Reference.*
CH_3—CH·COOEt MeCO COPh	Ammonia.	32, 33
	Aniline.	32
CH_3—CH·COOEt PhCO COPh	Ammonia.	14
	Aniline.	14
	o- and *p*-Toluidines.	18
	m-Xylidine.	18
	α- and β-Naphthylamines.	18
	o-Aminophenol.	18
	p-Phenylenediamine.	18
COOEt·CH—CH·COOEt MeCO COMe	Ammonia.	1, 3, 20, 23, 24
	Methylamine.	1, 8
	Glycine.	8
	Aniline.	1
	p-Toluidine.	1
	α-Naphthylamine.	8
	β-Naphthylamine.	1
	3-Amino-7-nitro-2-methyl-4-quinazolone.	38
	4-Aminodiphenic acid.	35
	4 : 4′-Diaminodiphenic acid.	35
	m-Tolylenediamine.	8
	Hydroxylamine.	4, 8
	Hydrazine.	27
	2 : 4-Dichlorophenylhydrazine.	39
	Methylphenylhydrazine.	8
	Benzoylhydrazine.	27
	Phenacetylhydrazine.	27
	p-Tolylhydrazones of mesoxalic hydrazido-ester and dihydrazide.	36
COOEt·CH—CH·COOEt PhCO COPh	Ammonia.	21
	Phenylhydrazine.	21
COOEt·CH—CH·CH_3·COOEt MeCO COMe	Ammonia.	7

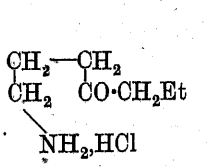
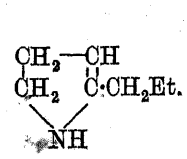
References.

[1] Knorr, *Ber.*, 1885, **18**, 299–304. [2] Paal, *ibid.*, p. 367. [3] Knorr, *ibid.*, p. 1558. [4] *Idem*, *ibid.*, p. 1569. [5] Paal, *ibid.*, p. 2254. [6] Lederer and Paal, *ibid.*, pp. 2591–2598. [7] Knorr, *ibid.*, 1886, **19**, 48. [8] *Idem*, *Ann.*, 1886, **236**, 296–314. [9] Gabriel, *Ber.*, 1886, **19**, 840. [10] Paal and Schneider, *ibid.*, pp. 3156–3163. [11] Baumann, *ibid.*, 1887, **20**, 1486. [12] Hollemann, *ibid.*, p. 3359. [13] *Idem*, *Rec. trav. chim.*, 1887, **6**, 60. [14] Kapf and Paal, *Ber.*, 1888, **21**, 1491, 3060. [15] Garrett, *ibid.*, p. 3107. [16] Knorr, *ibid.*, 1889, **22**, 170. [17] Magnanini and Angeli, *ibid.*, p. 855. [18] Paal and Braikoff, *ibid.*, pp. 3086–3095. [19] Smith, *J. C. S.*, 1890, **57**, 645. [20] Curtius, *J. pr. Chem.*, 1894, **50**, 508. [21] Knorr and Schmidt, *Ann.*, 1896, **293**, 107, 109. [22] Tiemann and Semmler, *Ber.*, 1897, **30**, 434. [23] Paal and Härtel, *ibid.*, p. 1995. [24] Knorr and Rabe, *ibid.*, 1900, **33**, 3801. [25] Kehrer, *ibid.*, 1901, **34**, 1266. [26] Harries, *ibid.*, p. 1496. [27] Bülow, *ibid.*, 1902, **35**, 4311–4320. [28] Harries, *ibid.*, p. 1180. [29] Kehrer, *ibid.*, p. 2009. [30] Korschun, *ibid.*, 1905, **38**, 1128; 1904, **37**, 2191. [31] Reissert and Engel, *ibid.*, 1905, **38**, 3291, 3293. [32] Borsche and Fels, *ibid.*, 1906, **39**, 1927. [33] *Idem*, *ibid.*, pp. 3879, 3883. [34] Bülow, *ibid.*, p. 4107. [35] Schmidt and Schall, *ibid.*, 1907, **43**, 3002. [36] Bülow, *ibid.*, p. 4329. [37] Borsche and Titsingh, *ibid.*, p. 5011. [38] Bogert and Klaber, *J. A. C. S.*, 1908, **30**, 807. [39] Bülow, *Ber.*, 1918, **51**, 414. [40] Blaise, *Compt. rend.*, 1920, **171**, 34. [41] Willstätter and Pfannenstiel, *Ann.*, 1921, **422**, 14. [42] Willstätter and Bommer, *ibid.*, p. 23. [43] Karrer and Smirnoff, *Helv. Chim. Acta*, 1922, **5**, 832.

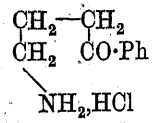
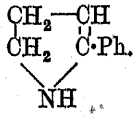
2. From γ-aminoketones or γ-ketoamides : 

Gabriel[1] prepared by the phthalimide method a series of α-, β-, γ-, δ- and ε-aminoketones. In the case of the γ- and δ-compounds, the free bases could not be isolated, condensation occurring at once, sometimes even in acid solution, to give pyrrolines and tetrahydropyridines respectively. α-Propyl- and α-phenyl-pyrrolines were obtained as follows :

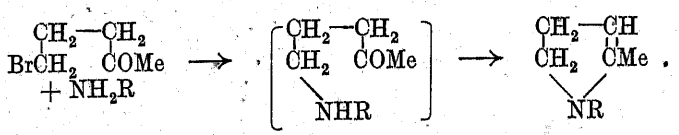
i. $C_6H_4<^{CO}_{CO}>N\cdot[CH_2]_3\cdot COCl + NaCEt(COOEt)_2$

$\longrightarrow C_8H_4O_2{:}N\cdot[CH_2]_3\cdot CO\cdot CEt(COOEt)_2 \xrightarrow{HCl}$  $\xrightarrow{NaOH}$ 

ii. $C_6H_4<^{CO}_{CO}>N\cdot[CH_2]_3\cdot COCl + C_6H_6 + AlCl_3$

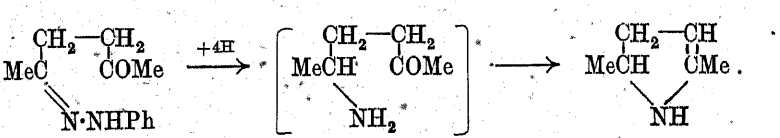
$\longrightarrow C_8H_4O_2{:}N\cdot[CH_2]_3\cdot CO\cdot Ph \xrightarrow{HCl}$  $\xrightarrow{NaOH}$ 

Hielscher[2] obtained pyrrolines by the action of ammonia and methylamine upon γ-bromopropyl methyl ketone[3] :

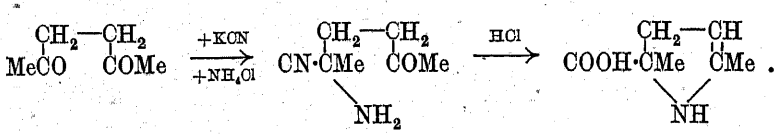


(R = H or Me.)

The reduction of acetonylacetone phenylhydrazone gives aniline and 2 : 5-dimethylpyrroline[4] :



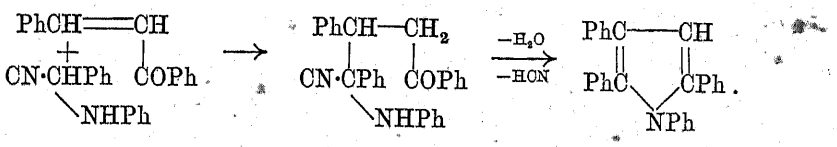
Another method of introducing a γ-amino-group is the application of the Strecker amino-acid synthesis to γ-diketones. Thus acetonylacetone is converted into dimethylpyrroline-carboxylic acid[5] :



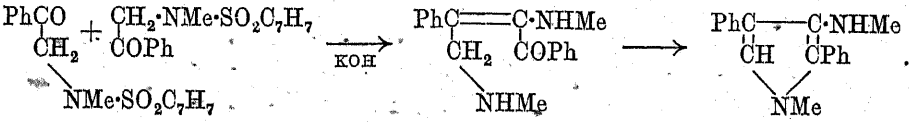
A secondary aminoketone was isolated by Clarke and Lapworth[6] by the action of benzal-

[1] *Ber.*, 1908, **41**, 513, 1127, 2010 ; 1909, **42**, 1264.
[2] *Ibid.*, 1898, **31**, 277.
[3] See also Mascarelli and Testoni, *Gazz.*, 1903, **33**, ii, 312.
[4] Tafel, *Ber.*, 1889, **22**, 1858.
[5] Zelinsky and Schlesinger, *ibid.*, 1907, **40**, 2886.
[6] *J. C. S.*, 1907, **91**, 704.

acetophenone upon the addition product from benzalaniline and HCN. It is converted into a pyrrole by gentle warming:



Phenacylmethylamine, liberated by the action of KOH upon its toluenesulphonyl derivative, at once condenses to an unsaturated γ-aminoketone, which may be isolated, together with the corresponding pyrrole [1]:

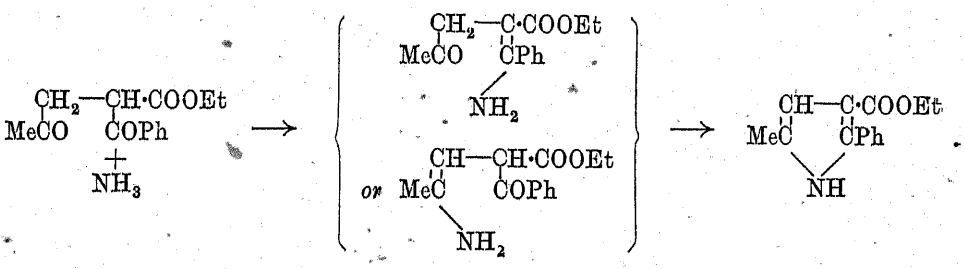


In a similar manner, *p*-tolacylamine hydrochloride,

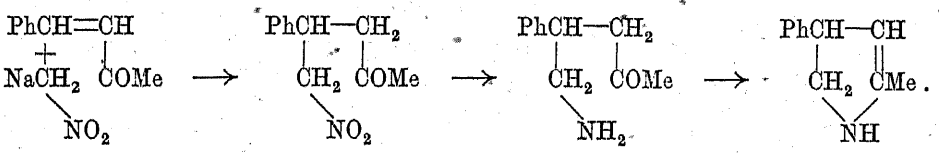
$$Me{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}NH_2{,}HCl,$$

is converted by KOH into 2 : 4-ditolyl-3-aminopyrrole.[2]

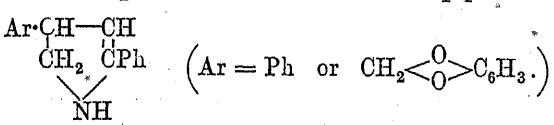
The ammonia derivative of α-benzoyl-lævulic ester is, according to either of the alternative formulæ, a γ-amino-ketone. It readily anhydrises to the pyrrole compound [3]:



Kohler and Drake [4] have used sodio-nitromethane in the synthesis of γ-nitroketones. These are reducible to γ-aminoketones, which condense at once, or on treatment with benzenesulphonyl chloride, to pyrrolines:

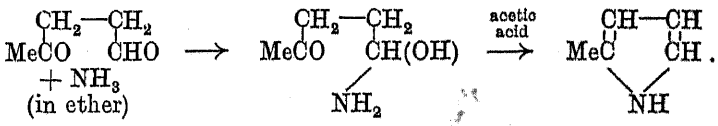


The same series of reactions was performed with benzal- and piperonal-acetophenones, giving:

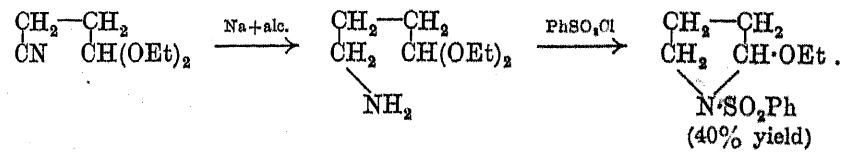


[1] Gabriel, *Ber.*, 1914, **47**, 1336.
[2] Rüdenburg, *ibid.*, 1913, **46**, 3555.
[3] Borsche and Fels, *ibid.*, 1906, **39**, 1922.
[4] *J. A. C. S.*, 1903, **45**, 2144.

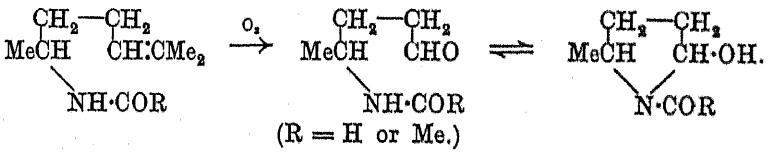
The aldehyde-ammonia obtained from lævulic aldehyde is cyclised by warming with dilute acetic acid[1]:



Wohl, Schäfer and Thiele[2] converted γ-aminobutyracetal into a pyrrolidine by treatment with benzenesulphonyl chloride:

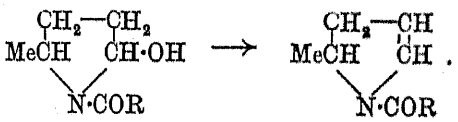


Acylated γ-aminoaldehydes have further been studied by Helferich and Dommer,[3] who oxidised with ozone the formyl, acetyl, propionyl, and benzoyl derivatives of the unsaturated amine, $NH_2 \cdot CHMe \cdot CH_2 \cdot CH_2 \cdot CH{:}CMe_2$. The formyl and acetyl compounds gave on ozonisation an equilibrium mixture of aminoaldehyde and hydroxypyrrolidine:



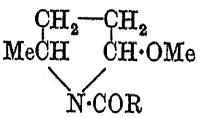
(R = H or Me.)

In the case of the propionyl and benzoyl derivatives, the product was a pyrroline:



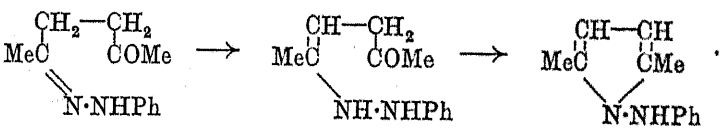
(R = ·C_3H_7 or Ph.)

Ring-closure occurred when the aminoaldehyde was treated with 1–2% methyl-alcoholic HCl, a methoxypyrrolidine being formed:



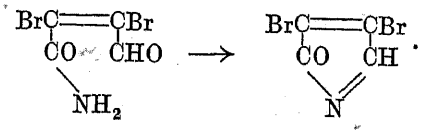
(R = Me or ·C_3H_7.)

The *N*-phenylamino-2 : 5-dimethylpyrrole obtained by Arbusov[4] by heating the phenylhydrazone of acetonylacetone with Cu_2Cl_2 at 180–190° probably results from an intermediately formed γ-hydrazinoketone (cf. p. 80):

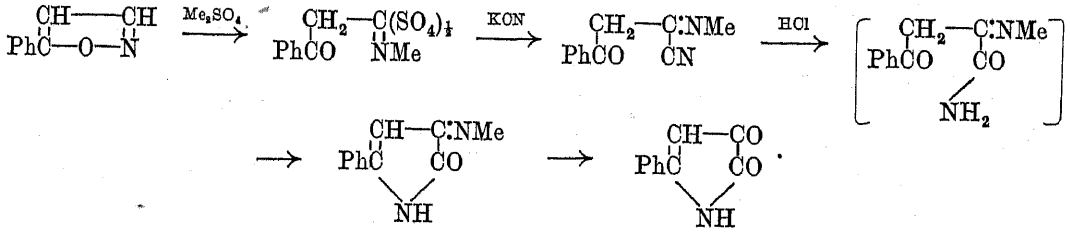


[1] Harries, *Ber.*, 1898, 31, 44.
[2] *Ibid.*, 1905, 38, 4154, 4159.
[3] *Ibid.*, 1920, 53, 2004.
[4] *J. Russ. Phys. Chem. Soc.*, 1913, 45, 699.

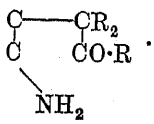
The amides of γ-keto-acids are readily anhydrised to pyrrole derivatives. Mucobromamide warmed with conc. H_2SO_4 gives 3 : 4-dibromopyrrolenone [1] :



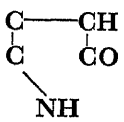
A similar reaction accounts for the production of phenyldiketopyrroline from phenyl*iso*oxazole methosulphate by the successive action of KCN and alcoholic HCl [2] :



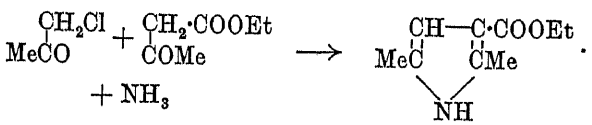
The examples given in this section seem to indicate that pyrrole formation occurs easily in the case of enolisable γ-aminoketones, but much less readily with γ-aminoaldehydes, especially if enolisation is precluded. It is probable that no ring-closure would occur in the case of non-enolisable γ-aminoketones of the type



This synthesis is thus a special case of the γ-amino-alcohol method (sect. 8).

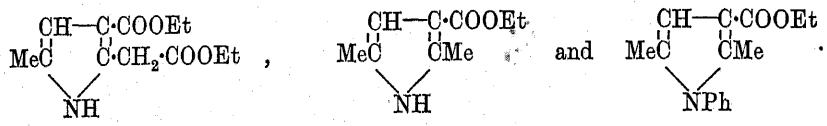
3. From chloroacetone, β-keto-esters and amines: 

Hantzsch [3] condensed chloroacetone with acetoacetic ester and ammonia and obtained a 20% yield of 2 : 5-dimethylpyrrole-3-carboxylic ester :

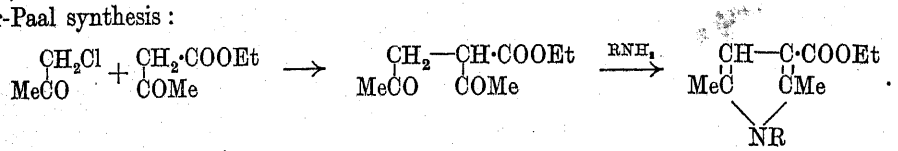


[1] Bistrzycki and Herbst, *Ber.*, 1901, **34**, 1020.
[2] Mumm and Münchmeyer, *ibid.*, 1910, **43**, 3335, 3345. Cf. p. 78.
[3] *Ibid.*, 1890, **23**, 1474.

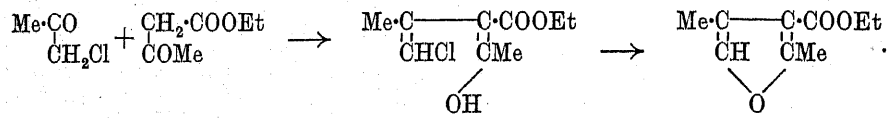
The method was extended by Feist and Molz [1] to acetonedicarboxylic ester, while Feist, Widmer and Dubosc [2] in addition used acetoacetic ester with ammonia and with aniline, the products obtained being:



Feist has discussed the mechanism of the reaction.[3] He considered that the first product was a γ-diketone, from which the pyrrole could be obtained by the action of amines as in the Knorr-Paal synthesis:

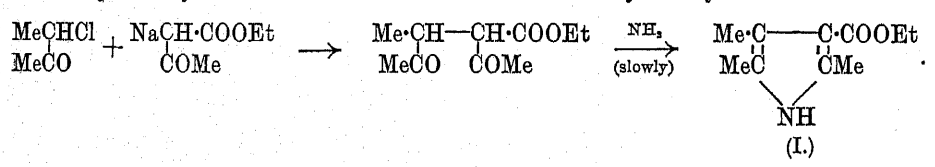


At the same time, there is formed a furane derivative. Curiously enough, this by-product is not the furane corresponding to the pyrrole, but is derived from a different intermediate [4]:

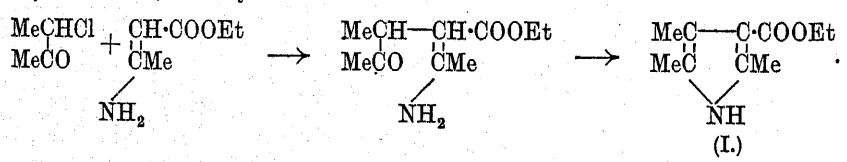


The furane is the main product when acetonedicarboxylic ester is used, and also when chloroethylidene-acetoacetic ester is substituted for the mixture of chloroacetone and acetoacetic ester.[5]

Korschun,[6] who used the method for 2 : 3 : 5-trimethylpyrrole-4-carboxylic ester (I), has called in question Feist's conclusions. He synthesised the intermediate diketone in the case of α-chloroethyl methyl ketone and found that it reacted only slowly with ammonia:

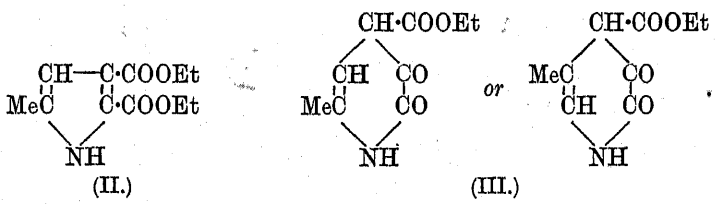


On the other hand, the action of ammonia upon acetoacetic ester in the cold readily gives β-aminocrotonic ester, whether the chloroketone is present or not. The pyrrole is only formed after heating. Korschun therefore considers that the course of the reaction is as originally suggested by Hantzsch, namely:



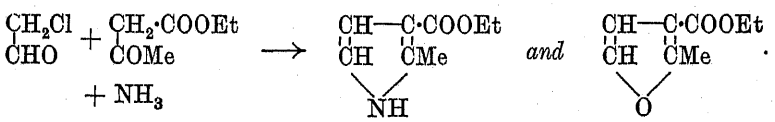
[1] *Ber.*, 1899, **32**, 1766.
[2] *Ibid.*, 1902, **34**, 1545–1556.
[3] *Ibid.*, **35**, 1538.
[4] Cf. also Plancher and Albini, *R. A. L.*, 1904, [v], **13**, i, 39–43.
[5] *Idem, loc. cit.*
[6] *Ber.*, 1905, **38**, 1125.

From chloroacetone, ammonia and oxalacetic ester Feist, Widmer and Dubosc [1] obtained only a small amount of the pyrrole (II), the main product being a pyridine derivative (III):



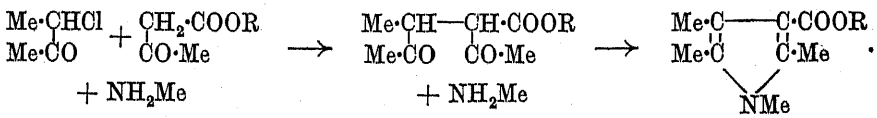
(II.) (III.)

Chloroacetaldehyde, or dichloroethyl ether (which readily passes into chloroacetaldehyde on heating), has been used in place of chloroacetone by Benary [2]:



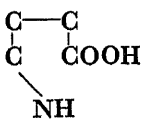
The furane by-product is in this case the analogue of the pyrrole, no isomeride being possible.

Korschun and Roll [3] have recently used the Hantzsch method for the preparation of 1 : 2 : 3 : 5-tetramethylpyrrole-4-carboxylic esters:

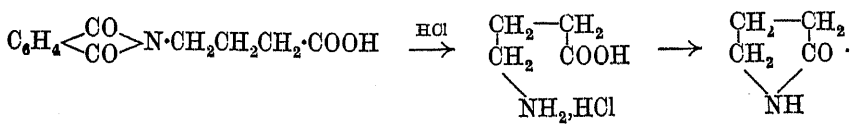


Methylamine and *p*-toluidine have similarly been employed with chloroacetone and acetoacetic ester by H. Fischer and Smeykal.[4]

4. From γ-amino-acids or -esters:

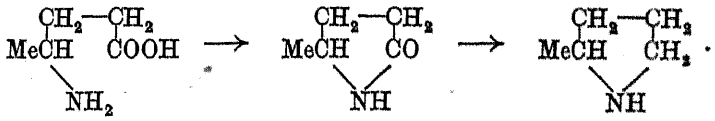


γ-Amino-acids readily lose water when heated and form the corresponding lactams, which are derivatives of pyrrolidone. The lactam of γ-aminobutyric acid, prepared by Gabriel,[5] is pyrrolidone itself:



[1] *Ber.*, 1902, **35**, 1552. [2] *Ibid.*, 1911, **44**, 493; see also Plancher and Albini, *loc. cit.*
[3] *Bull. Soc. chim.*, 1923, [iv], **33**, 1107. [4] *Ber.*, 1923, **56**, 2373. [5] *Ibid.*, 1889, **22**, 3338.

Tafel [1] reduced the lactam of γ-aminovaleric acid to 2-methylpyrrolidine:

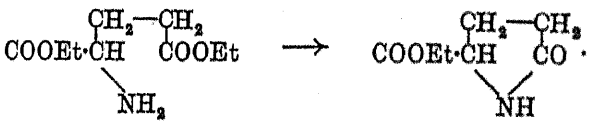


Glutamic acid (α-aminoglutaric acid) may be converted into glutimide by heating the ammonium salt at 185–190° or by heating the acid or acid ester with urea at 125–150° [2]:

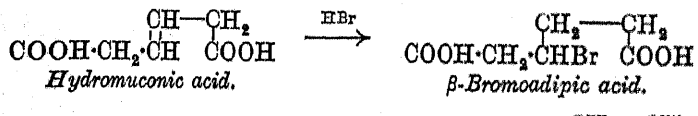


Glutimide.

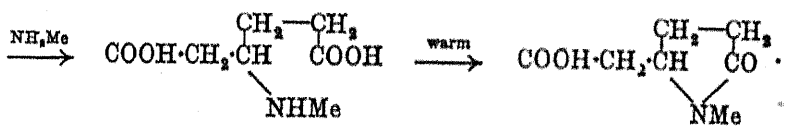
The corresponding 2-pyrrolidone-5-carboxylic ester has been obtained in 80% yield by heating glutamic ester for 20 minutes at 160–170° [3]:



Willstätter's synthesis of ecgonic acid from β-bromoadipic acid and methylamine is a further example [4]:

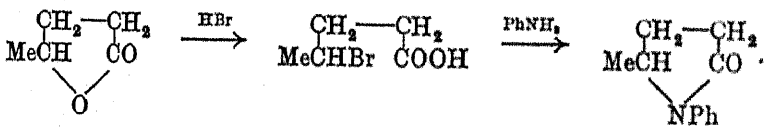


Hydromuconic acid. *β-Bromoadipic acid.*

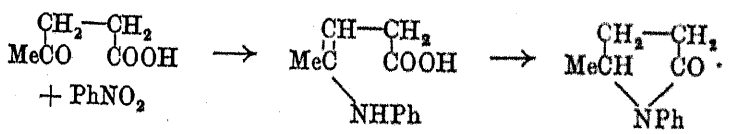


Ecgonic acid.

Emmert [5] used a similar method for the preparation of 1-phenyl-2-methyl-5-pyrrolidone from valerolactone:

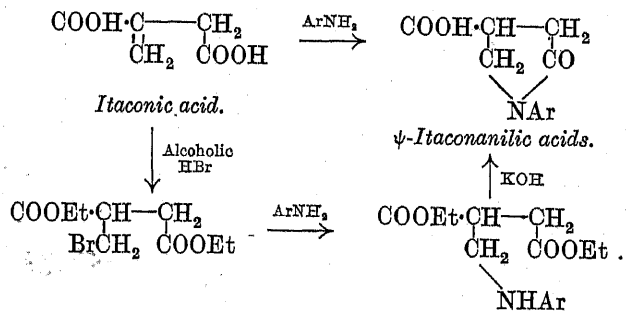


He obtained the same compound by electrolytic reduction of a mixture of nitrobenzene and lævulic acid in alcoholic H_2SO_4:



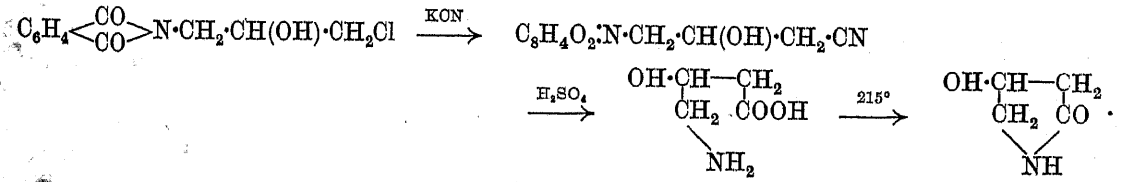
[1] *Ber.*, 1887, **20**, 250; 1889, **22**, 1860, 1865.
[2] Habermann, *Ann.*, 1875, **179**, 251; Haitinger, *Monatsh.*, 1882, **3**, 228; Wolff, *Ann.*, 1890, **260**, 124; Anderlini, *Gazz.*, 1890, **19**, 99; Menozzi and Appiani, *ibid.*, 1894, **23**, i, 370.
[3] Chiles and Noyes, *J. A. C. S.*, 1922, **44**, 1805. [4] *Ber.*, 1901, **34**, 1818. [5] *Ibid.*, 1907, **40**, 912.

Itaconic acid, $CH_2{:}C(COOH)\cdot CH_2\cdot COOH$, condenses with arylamines to give ψ-itaconanilic acids, the constitution of which was elucidated by Anschütz [1]:

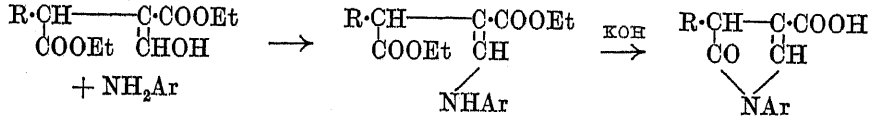


(Ar = Ph, *p*-C_7H_7·, α-$C_{10}H_7$·, ·NHPh.)

Tomita [2] has used the phthalimide method for the preparation of γ-amino-β-hydroxybutyric acid, which at 215° yields the lactam:

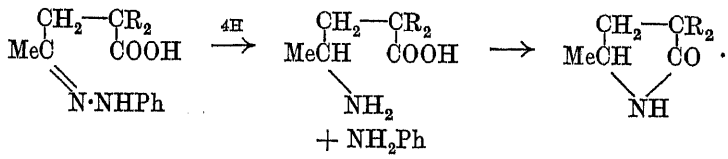


A series of unsaturated γ-amino-esters was prepared by Carrière [3] from hydroxymethylenesuccinic esters and amines. Hydrolysis with conc. KOH converts the products into pyrrolones:



(R = H, Et; Ar = Ph, *p*-C_7H_7·, $PhCH_2$·.)

A γ-amino-group may also be conveniently introduced by energetic reduction of the phenylhydrazone of a γ-keto-acid. Thus Tafel [4] obtained γ-aminovaleric acid from lævulic acid, and Haller and Bauer [5] treated the phenylhydrazone of mesitonic acid similarly:

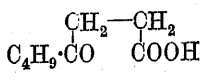


(R = H (lævulic) or Me (mesitonic).)

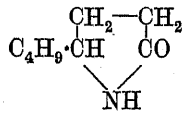
This method seems to fail in the case of β-valerylpropionic acid (I), from which Blaise and

[1] *Ann.*, 1889, **254**, 148, 149.
[2] *Z. physiol. Chem.*, 1923, **124**, 253.
[3] *Ann. Chim.*, 1922, [ix], **17**, 38–122.
[4] *Ber.*, 1886, **19**, 2415.
[5] *Compt. rend.*, 1914, **158**, 1086.

Houillon * synthesised a compound related to that obtained by distilling octamethylene diamine hydrochloride. The product was not, however, the expected 2-butylpyrrolidone (II) [1]:

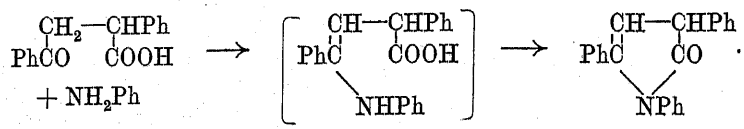


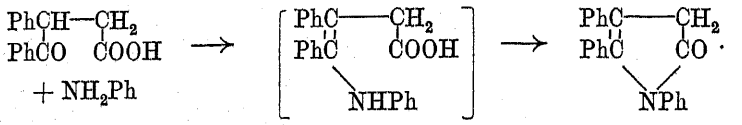
(I.)



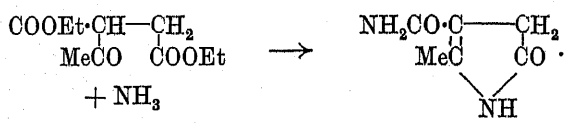
(II.)

Certain γ-keto-acids give pyrrolones directly in good yield by the action of aniline. *E.g.*: [2]

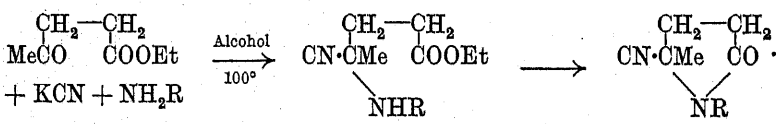




Similarly, Ruhemann and Hemmy [3] obtained 2-methyl-5-pyrrolone-3-carboxylamide from acetylsuccinic ester and alcoholic NH_3:



The application of the Strecker amino-acid synthesis to keto-acids (lævulic acid) has been the subject of a series of investigations by Kühling [4] and by Weber [5]:



(R = H, phenyl, *o*-, *m*-, *p*-tolyl, 3-*o*-xylyl, 4-*o*-xylyl, 4-*m*-xylyl, *p*-xylyl, α-, β-naphthyl, benzyl, or *p*-X·C_6H_4, where X is Cl, Br, I, ·CN or ·COOEt.)

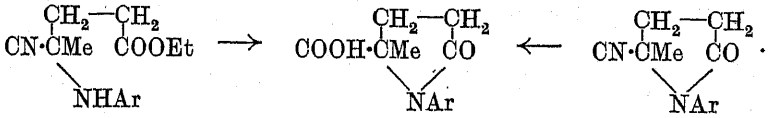
From benzylamine both the lactam and the aminonitrile were obtained, the latter being easily converted into the former by gentle heating. The yields of lactam varied considerably, as the following table shows:

Arylamine.	*Lactam.*	*Arylamine.*	*Lactam.*
p-Toluidine	100%	*o*-Toluidine	40%
3-*o*-Xylidine	80	β-Naphthylamine	27
4-*o*-Xylidine	80	α-Naphthylamine	20
m-Toluidine	60	*p*-Xylidine	20
4-*m*-Xylidine	50		

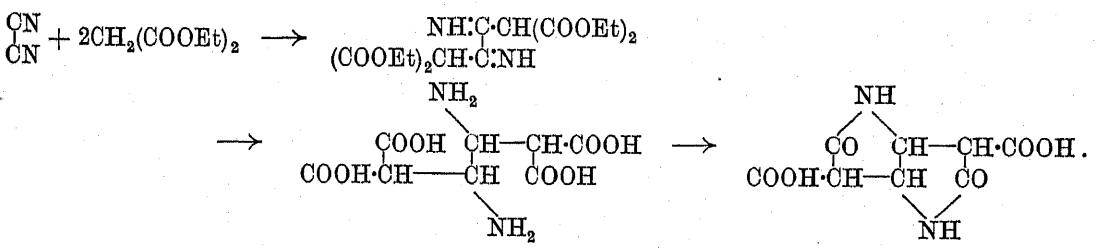
[1] Hess, *Ber.*, 1919, **52**, 1636.
[2] Almström, *Ann.*, 1913, **400**, 140, 145.
[3] *J. C. S.*, 1897, **71**, 330.
[4] *Ber.*, 1889, **22**, 2366; Kühling and Falk, *ibid.*, 1905, **38**, 1215; Kühling and Frank, *ibid.*, 1909, **42**, 3954.
[5] *Ibid.*, 1907, **40**, 4044.

* See p. 62.

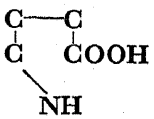
Weber was unable to obtain the products from halogenated anilines in sufficient purity to distinguish between amino-nitrile-ester and lactam, whilst cyanoaniline gave only an oil. From *p*-aminobenzoic ester the product was the aminonitrile-ester. All the products (except that from cyanoaniline) were converted into pyrrolidones (*i.e.* lactams) when the nitrile group was hydrolysed with conc. HCl:



A double γ-amino-acid cyclisation is recorded by Traube[1]:

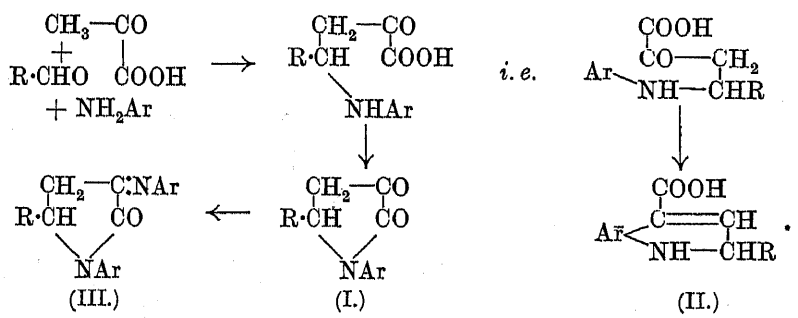


5. From α-keto-acids (or -esters), aldehydes and amines:



The syntheses in this section are conveniently considered under two heads, (i) from pyruvic acids, (ii) from oxalacetic ester or acylpyruvic esters.

(i) *Pyruvic acids.* In Döbner's quinoline synthesis (p. 256) from pyruvic acid, aldehydes and arylamines the first product has been shown by Borsche[2] to be a γ-amino-acid, Ar·NH·CHR·CH_2·CO·COOH. This by further condensation may give a diketopyrrolidine (I) or a dihydroquinoline (II), and in the presence of excess of base the former is converted into its β-anil (III):



[1] *Ber.*, 1902, **35**, 4124.

[2] *Ibid.*, 1908, **41**, 3884; 1909, **42**, 4072.

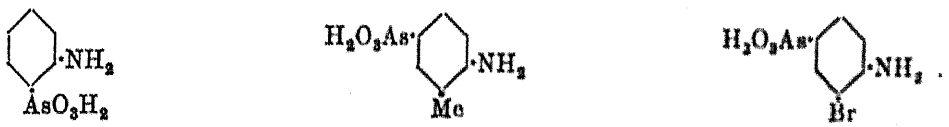
Döbner [1] found that in the case of the naphthylamines III becomes the main product when the reaction is performed in ether solution. Benzalaniline and pyruvic acid in ether give a similar result.[2]

Borsche [3] has studied the behaviour of a large number of arylamines in this reaction and has shown that *p*-chloroaniline, *m*- and *p*-nitroanilines and *m*- and *p*-aminoacetophenones give almost exclusively the diketopyrrolidine or its anil. The reaction fails with *o*-chloro- and *o*-nitro-anilines, only the Schiff's base being formed. Substituted pyruvic acids,

$$R{\cdot}CH_2{\cdot}CO{\cdot}COOH,$$

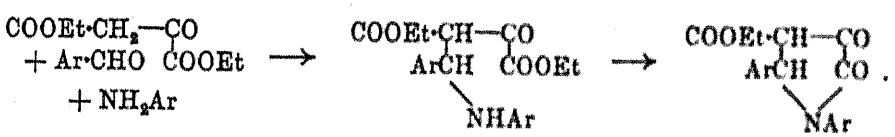
where R is phenyl, *o*-nitrophenyl or benzoyl, yield only the pyrrole compound and benzylpyruvic acid gives only small amounts of quinolines.

Borsche's conclusions have been confirmed by the recent work of Johnson and Adams,[4] who have applied the reaction to arsanilic acids in the hope of preparing cinchoninic acids containing arsenic. In every case the product was a Schiff's base or a diketopyrrolidine. The reaction failed with aliphatic aldehydes (paraldehyde and butyraldehyde) and only the Schiff's bases resulted when benzaldehyde and pyruvic acid were condensed with arsanilic acids in which a substituent *ortho* to the $\cdot NH_2$ was present, namely :

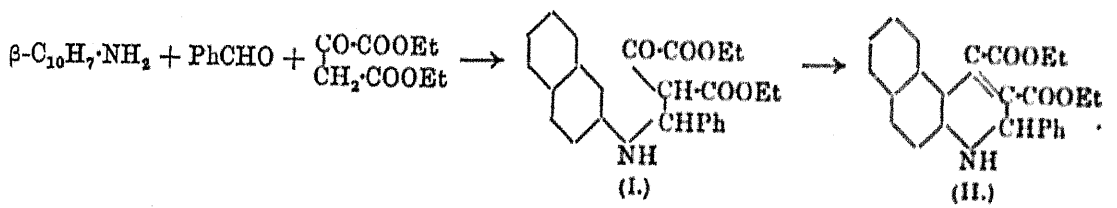


Ortho-substitution in the aldehyde did not prevent ring-closure.

(ii) *Oxalacetic and other acylpyruvic esters :* Schiff and Bertini [5] found that diketopyrrolidines were obtained by heating on the water-bath a mixture of oxalacetic ester, and aromatic amine and an aromatic aldehyde :



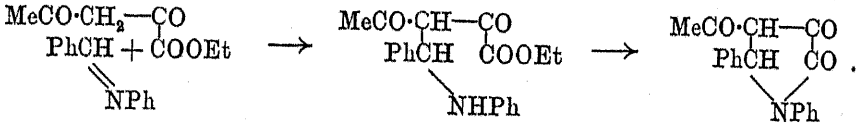
The reaction was further investigated by Simon and Conduché.[6] They showed that β-naphthylamine gives no pyrrole derivative, but a compound (I) which is converted by conc. H_2SO_4 into a dihydronaphthoquinoline (II) :



[1] *Ann.*, 1887, **242**, 265; 1888, **249**, 98; **281**, 1. [2] Garzarolli-Thurnlackh, *Monatsh.*, 1890, **20**, 480.
[3] *Loc. cit.* [4] *J. A. C. S.*, 1921, **43**, 2255; 1923, **45**, 1307. [5] *Ber.*, 1897, **30**, 601.
[6] *Compt. rend.*, 1904, **138**, 977; **139**, 211, 297; *Ann. Chim.*, 1907, [viii], **12**, 5–58; Simon and Maugin, *ibid.*, 1908, [viii], **13**, 361.

β-Naphthylamine behaves similarly with oxalacetic ester and anisaldehyde or *m*-nitrobenzaldehyde. With piperonal, on the other hand, a diketopyrrolidine is formed, while vanillin and salicylaldehyde yield neither. The reaction fails with α-naphthylamine.

Schiff and Gigli [1] extended the reaction to acetylpyruvic ester (acetone-oxalic ester), from which they prepared 1 : 2-diphenyl-3-acetyldiketopyrrolidine :

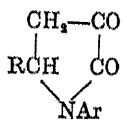


Cinnamoylpyruvic ester, $PhCH{:}CH{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}COOEt$, and benzoylpyruvic ester, $PhCO{\cdot}CH_2{\cdot}CO{\cdot}COOEt$, behaved similarly.

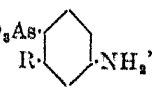
The researches of Borsche [2] upon the formation of pyrrole derivatives by the condensation of benzoylpyruvic ester and aniline with benzaldehyde and with anisaldehyde have already been mentioned above. The product obtained by Schiff and Gigli from benzoylpyruvic ester and benzal-β-naphthylamine is doubtless a quinoline and not a diketopyrrolidine.

Acetylpyruvic ester gives pyrrolidines with *p*-aminophenol and *p*-iodoaniline in the presence of benzaldehyde, while oxalacetic ester fails. In alcohol both esters fail to react with aldehydes and *ortho*-substituted anilines, but diketopyrrolidines may be obtained even in these cases by using benzene instead of alcohol as solvent.

Diketopyrrolidines have been prepared by the following condensations :

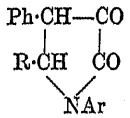
Aldehyde, R·CHO.	*Arylamine*, $ArNH_2$.	*Reference.*
(a) *From pyruvic acid :* 		
Benzaldehyde	Aniline.	4
	m-, *p*-Chloroanilines.	6
	m-, *p*-Nitroanilines.	6
	o-Toluidine.	1
	p-Aminoacetophenone.	6
	m-, *p*-Aminobenzoic acids.	1
	Arsanilic acid.*	9
	2-Methylarsanilic acid.*	9
	2-Methoxyarsanilic acid.*	9
Cuminaldehyde	Aniline.	1
Furfural	Aniline.	1
o-, *p*-Methoxybenzaldehydes, Piperonal, *p*-Chlorobenzaldehyde, Salicylaldehyde, *p*-Dimethylaminobenzaldehyde, Cinnamaldehyde	Arsanilic acid.	9

[1] *Ber.*, 1898, **31**, 1306. [2] *Ibid.*, 1909, **42**, 4084.
[3] D.R.-P. 283305. [4] D.R.-P. 280971.

*  , where R = H, Me or ·OMe.

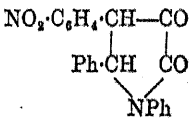
Aldehyde, R·CHO	*Arylamine*, $ArNH_2$	*Reference.*

(b) *From phenylpyruvic acid :*



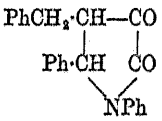
Formaldehyde	Aniline.	6
Benzaldehyde	Aniline.	6
	o-, *m*-, *p*-Toluidines.	6
	m-Nitroaniline.	6
p-Nitrobenzaldehyde	Aniline.	6
Salicylaldehyde	Aniline.	6

(c) *From o-nitrophenylpyruvic acid :*



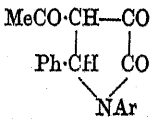
Benzaldehyde	Aniline.	6

(d) *From benzylpyruvic acid :*



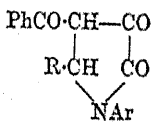
Benzaldehyde	Aniline.	6

(e) *From acetylpyruvic acid :*



Benzaldehyde	Aniline.	3
	p-Aminophenol.	8
	p-Iodoaniline.	8
	m-, *p*-Toluidines.	8
	o-Toluidine.	7
	o-Anisidine.	7
	p-Phenetidine.	8
	8-Aminoquinoline.	7
	4-Aminoantipyrine.	7
p-Dimethylaminobenzaldehyde	*p*-Toluidine.	7
Piperonal	Aniline.	7
Furfural	Aniline.	7

(f) *From benzoylpyruvic acid or ester :*



Benzaldehyde	Aniline.	1, 6
	p-Toluidine.	8
	o-Anisidine.	7
Anisaldehyde	Aniline.	6

Aldehyde, R·CHO	*Arylamine*, $ArNH_2$	*Reference.*
(g) *From cinnamoylpyruvic* acid : $PhCH{:}CH{\cdot}CO{\cdot}CH{-}CO$	$Ph{\cdot}CH\ CO$	
	NPh	
Benzaldehyde	Aniline.	3

References.

[1] Döbner, *Ann.*, 1887, **242**, 284, 295; 1888, **249**, 102; 1894, **281**, 4. [2] Schiff and Bertini, *Ber.*, 1897, **30**, 601. [3] Schiff and Gigli, *ibid.*, 1898, **31**, 1307. [4] Garzarolli-Thurnlackh, *Monatsh.*, 1899, **20**, 480. [5] Simon and Conduché, *Compt. rend.*, 1904, **138**, 977; **139**, 211, 297; *Ann. Chim.*, 1907, [viii], **12**, 5–58; Simon and Maugin, *ibid.*, 1908, [viii], **13**, 361. [6] Borsche, *Ber.*, 1908, **41**, 3884; 1909, **42**, 4072. [7] D.R.-P. 280971. [8] D.R.-P. 283305. [9] Johnson and Adams, *J. A. C. S.*, 1921, **43**, 2255; 1923, **45**, 1307.

6. Preparation of succinimides and maleinimides : $\begin{matrix}C\text{———}C\\ \vert\quad\quad\vert\\ COOH\ COOH\end{matrix} + NH_2R$

A variety of methods may be used for the preparation of succinimides and maleinimides; these may be grouped as follows :

(*a*) *From succinic acid or anhydride and* NH_3 *or amines :* This is the usual method, and consists in heating a succinic acid or its anhydride with ammonia or a primary amine :

$$\begin{matrix}CH_2{\cdot}COOH\\ CH_2{\cdot}COOH\end{matrix} + NH_2R \longrightarrow \begin{matrix}CH_2\text{—}CO\\ CH_2\text{—}CO\end{matrix}\!\!>\!NR.$$

Thus Tafel and Stern [1] obtained methylsuccinimide in 75% yield by heating methylamine succinate at 200°. Koller [2] obtained good results by heating an aqueous suspension of succinic anhydride with aniline, *p*-toluidine or *β*-naphthylamine.

The first product of the action of a primary amine upon a succinic anhydride is usually a succinamic acid, which is converted into the imide by heat or by treatment with acetic anhydride,[3] with acetyl chloride [4] or with certain bases ; [5]

$$\begin{matrix}CH_2\text{—}CO\\ CH_2\text{—}CO\end{matrix}\!\!>\!O \xrightarrow{RNH_2} \begin{matrix}CH_2\text{—}CO\\ CH_2\text{—}COOH\end{matrix} NHR \longrightarrow \begin{matrix}CH_2\text{—}CO\\ CH_2\text{—}CO\end{matrix}\!\!>\!NR.$$

Komatsu obtained succinanil by heating the methylamine salt of succinamilic acid. Heat does not effect ring-closure if R is an aryl group carrying an *ortho* substituent.[6]

Hydroxylamine [7] and phenylhydrazine [8] behave like other primary amines.

[1] *Ber.*, 1900, **33**, 2232. [2] *Ibid.*, 1904, **37**, 1598.
[3] Bogert and Wise, *J. A. C. S.*, 1912, **34**, 693.
[4] Auwers, *Ann.*, 1899, **309**, 316. [5] Komatsu, *Zeats.*, 1909, ii, 983; cf. also p. 150.
[6] Ruggli, *Ann.*, 1917, **412**, 13. [7] Errera, *Gazz.*, 1895, **25**, ii, 25, 263.
[8] Levy and Englander, *Ann.*, 1887, **242**, 303; Michael and Palmer, *Amer. Chem. J.*, 1888, **9**, 180; Auger, *Ann. Chim.*, 1891, [vi,] **22**, 289; v. Auwers, *Ber.*, 1890, **23**, 3624; *Ann.*, 1896, **292**, 172.

Succinyl chloride, owing to its tendency to give unsymmetrical iminosuccinides (especially in reactions with ammonia and aliphatic amines), is less suitable than the anhydride for the preparation of succinimides.[1] It gives, however, with glycine ester a 52% yield of succinimino-acetic ester.[2]

The relative ease of formation of the *N*-substituted succinimides may be judged from the results of Miolati and Longo,[3] who found that the rate of hydrolysis by alkali was represented by the following figures :

Alkyl or aryl.	*k.*	*Alkyl or aryl.*	*k.*
$CHMe_2 \cdot CH_2 \cdot CH_2 \cdot$	0·0336	$Ph \cdot CH_2 \cdot$	0·276
$CH_3 \cdot CH_2 \cdot CHMe \cdot$	0·0372	$CH_2 : CH \cdot CH_2 \cdot$	0·282
$CHMe_2 \cdot CH_2 \cdot$	0·0388	$o\text{-}Me \cdot C_6H_4 \cdot$	0·856
$CH_3 \cdot CH_2 \cdot CH_2 \cdot$	0·055	$m\text{-}Me \cdot C_6H_4 \cdot$	1·098
$CHMe_2 \cdot$	0·068	$p\text{-}Me \cdot C_6H_4 \cdot$	1·12
$CH_3 \cdot CH_2 \cdot$	0·085	$Ph \cdot$	2·27
$CH_3 \cdot$	0·217		

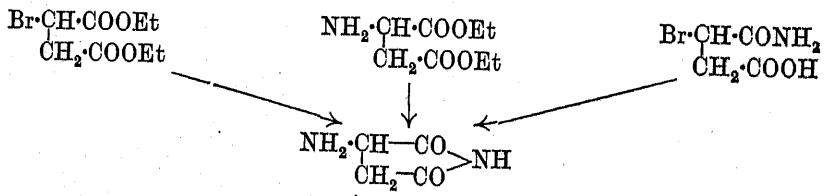
The hydroxy-group in malic acid is easily amidated; true malimides have, however, been prepared by careful heating of a mixture of malic acid and *o*-toluidine or *β*-naphthylamine,[4] and Arppe [5] as long ago as 1855 obtained malanil by the action of KOH upon malic anilide :

$$\begin{matrix} OH \cdot CH \cdot CONHPh \\ | \\ CH_2 \cdot COOH \end{matrix} \longrightarrow \begin{matrix} OH \cdot CH - CO \\ | \quad\quad > NPh. \\ CH_2 - CO \end{matrix}$$

The anilido-anil of citric acid is best prepared from the acetyl derivative of citric anhydride : [6]

$$\begin{matrix} CH_2 \cdot COOH \\ | \\ AcO \cdot C - CO \\ | \quad\quad > O \\ CH_2 - CO \end{matrix} + PhNH_2 \longrightarrow \begin{matrix} CH_2 \cdot CO \cdot NHPh \\ | \\ OH \cdot C - CO \\ | \quad\quad > NPh. \\ CH_2 - CO \end{matrix}$$

Aspartimide results from the action of alcoholic ammonia upon bromosuccinic ester at 105–110°,[7] upon aspartic ester [8] or upon bromosuccinamic acid at 160° : [9]

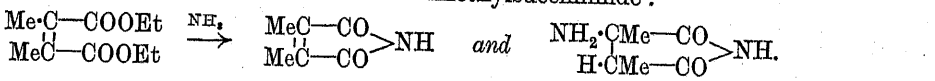


Aspartimide.

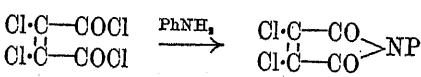
The condensation of succinamic ester in the presence of NaOEt gives only a small yield of succinimide.[10]

[1] Auger, *Bull.*, 1888, [ii], **49**, 345; *Ann. Chim.*, 1891, [vi], **22**, 289; Morell, *J. C. S.*, 1914, **105**, 1733.
[2] Curtius and Hechtenberg, *J. pr. Chem.*, 1922, **105**, 302.
[3] *R. A. L.*, 1894, [v], **3**, i, 597–605; 1895, **4**, i, 351–358.
[4] Bischoff and Nastvogel, *Ber.*, 1890, **23**, 2044, 2047.
[5] *Ann.*, 1855, **96**, 109.
[6] Bertram, *Ber.*, 1905, **38**, 1624.
[7] Körner and Menozzi, *Gazz.*, 1887, **17**, 173.
[8] Piutti, *ibid.*, 1888, **18**, 473.
[9] *Idem*, *Ber.*, 1896, **29**, 2069.
[10] de Mouilpied and Rule, *J. C. S.*, 1907, **91**, 178.

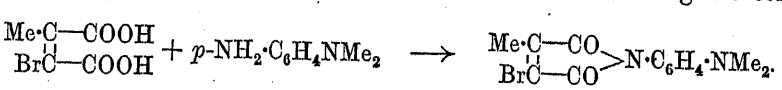
(*b*) *Maleinimides :* Maleic acid, its ester or its anhydride and the homologues of these are converted into imides by the action of alcoholic ammonia or by heating with primary amines. A second reaction also occurs—addition of NH_3 or amine at the double bond, with formation of an aminosuccinimide. Thus Molinari [1] obtained from pyrocinchonic ester and ammonia both the normal dimethylmaleinimide and aminodimethylsuccinimide :



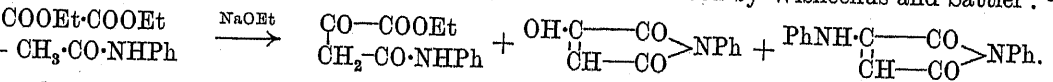
Hydrazine and maleic anhydride give, amongst other products, *N*-aminomaleinimide.[2] Anschütz and Beavis [3] prepared the phenylimide of dichloromaleic acid by the action of aniline upon the acid chloride :



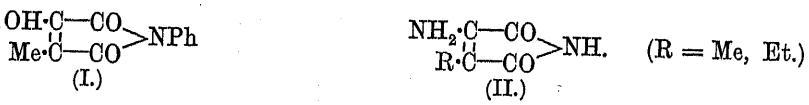
The bromine in bromocitraconic acid also remains unattacked during the conversion into imide : [4]



An interesting synthesis of hydroxymaleinimides is that described by Wislicenus and Sattler : [5]

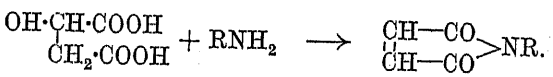


Acetyl-*p*-toluidine reacts similarly. From oxalic ester and propionanilide hydroxycitraconanil (I) was the only product isolated :



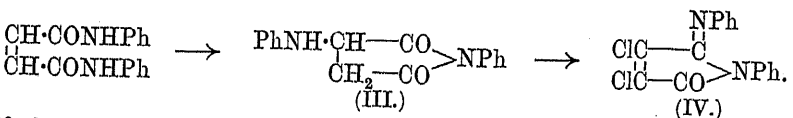
Ammonia reacts with oxalpropionic and oxalbutyric esters to give aminocitraconimides (II).[6]

Maleinimides are also obtained from the malates of ammonia or primary amines by heating at 160–200° :



Maleinimide itself was obtained in this way by Dessaignes,[7] * the methyl, ethyl and benzyl derivatives by Piutti [8] and Giustiniani,[9] and the anil by Anschütz and Wirtz.[10]

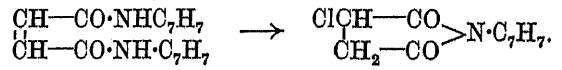
The action of PCl_5 (in benzene) upon the dianilides of maleic and tartaric acids has been investigated by Bischoff and Walden.[11] Maleic dianilide is converted first into phenylaspartanil (III) and by further action of PCl_5 into phenyliminodichloromaleinanil (IV) :



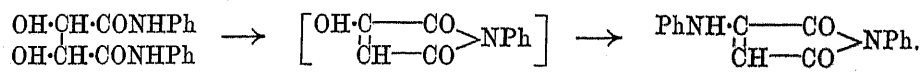
[1] *Ber.*, 1900, **33**, 1412.
[2] Curtius and Foersterling, *J. pr. Chem.*, 1895, **51**, 375, 387.
[3] *Ann.*, 1897, **295**, 34.
[4] Fichter and Tschudin, *J. pr. Chem.*, 1906, **74**, 297.
[5] *Ber.*, 1891, **24**, 1245.
[6] Wislicenus and Kiesewetter, *ibid.*, 1898, **31**, 194.
[7] *Compt. rend.*, 1850, **30**, 324.
[8] *Gazz.*, 1888, **18**, 483.
[9] *R. A. L.*, 1891, [iv], **7**, ii, 463; *Gazz.*, 1892, **22**, i, 169.
[10] *Ann.*, 1887, **239**, 141.
[11] *Ibid.*, 1894, **279**, 130–152.

* See, however, Ravenna and Bosinelli (*R. A. L.*, 1919, [v], **28**, ii, 113, 137).

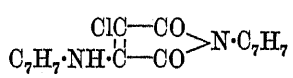
From the ditoluide and PCl_5 only chlorosuccino-*p*-tolil was obtained :



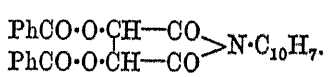
Tartaric dianilide reacts with PCl_5 to give phenylaminomaleinanil :



The ditoluide undergoes chlorination and yields *p*-tolylaminochloromaleinotolil (V).



(V.)



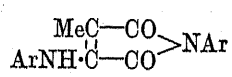
(VI.)

Using benzoyl chloride in place of PCl_5, Bischoff and Walden, from the di-α- and di-β-naphthalides, obtained tartrimides of the structure (VI).

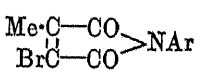
Fichter and Tschudin [1] have condensed citra- and mesa-dibromopyrotartaric acids (VII) with aniline, *p*- and *o*-toluidines and α- and β-naphthylamines. The products are of the types VIII (from citra-) and IX (from mesa-). The simple citradibromopyrotartrimides of the type X were obtained from *o*-toluidine and the naphthylamines by suitably moderating the temperature of action.



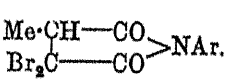
(VII.)



(VIII.)

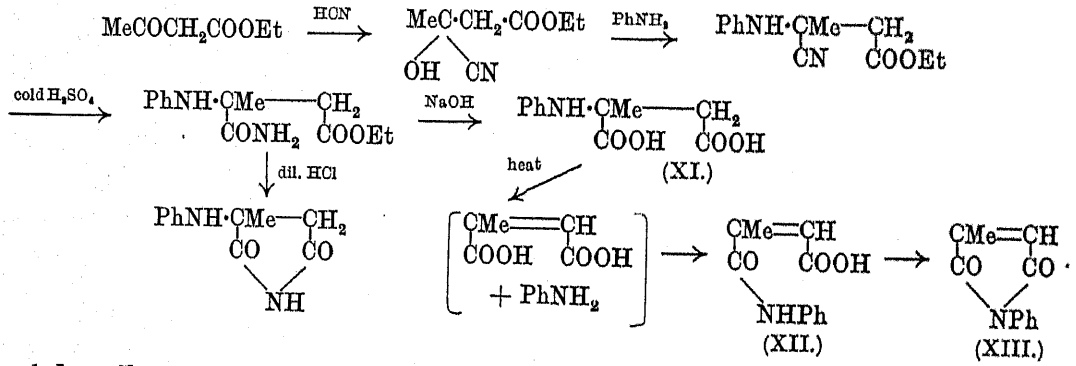


(IX.)



(X.)

The α-phenylamino-α-methylsuccinic acid (XI) synthesised by Schiller-Wechsler [2] undergoes an interesting condensation when heated at 180°.[3] Aniline is first eliminated, giving citraconic acid, which condenses with aniline in the usual way to form citraconanilic acid (XII) (Reissert's " pyranilpyroic acid ") and citraconanil (XIII) (Reissert's " pyranilpyroic lactone ") :



(XI.)

(XII.)

(XIII.)

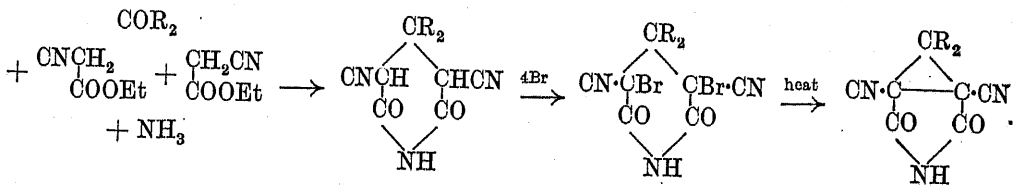
[1] *J. pr. Chem.*, 1906, **74**, 297; cf. Enzenauer, *Dissn. Basle*, 1900; Fichter and Preiswerk, *Ber.*, 1902, **35**, 1626.

[2] *Ibid.*, 1885, **18**, 1038.

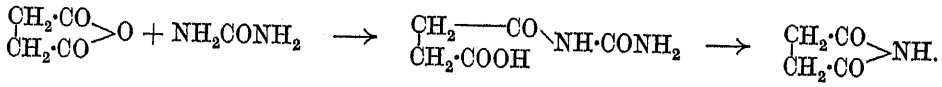
[3] Reissert and Tiemann, *ibid.*, 1886, **19**, 622; Reissert, *ibid.*, 1888, **21**, 1362, 1380, 1385, 1942; 1889, **22**, 2281; 1890, **23**, 542; Anschütz, *Ann.*, 1888, **246**, 115; 1889, **248**, 269; *Ber.*, 1888, **21**, 3252; 1890, **23**, 887, 2979.

(c) *Imides of alicyclic* 1 : 2-*dicarboxylic acids :* The anils of 1 : 2-dicarboxy-*cyclo*propane, -*cyclo*butane and -*cyclo*pentane derivatives are very easily formed by heating the acid anhydrides with aniline. They usually crystallise well and are useful for the characterisation of these acids.

The glutarimides prepared by Guareschi's method (see p. 202) from cyanacetic ester, ammonia and ketones are readily converted into imides of *cyclo*propane-1 : 2-dicarboxylic acids by treatment with bromine followed by heating at 110–120° in acetic or formic acid : [1]



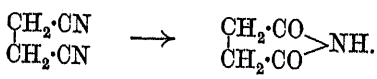
(d) *Use of urea in place of* NH_3 : Urea reacts with succinic anhydride to form succinuric acid, which on further heating is converted into succinimide : [2]



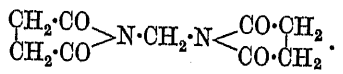
From succinic ester, urea and NaOEt Roeder [3] obtained succinimide in 50% yield, NaCNO being formed at the same time.

Maleinimide cannot be prepared by Dunlap's method,[4] but dichloro- and dibromo-maleic acids react normally.[5]

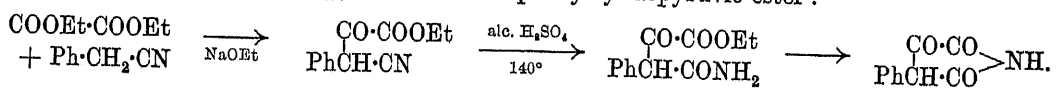
(e) *Hydrolysis of nitriles or nitrile-esters :* Ethylene dicyanide gives succinimide when heated with dilute H_2SO_4 at 165–175° : [6]



With trioxymethylene in acetic acid ethylene dicyanide yields *N* : *N'*-methylenedisuccinimide : [7]

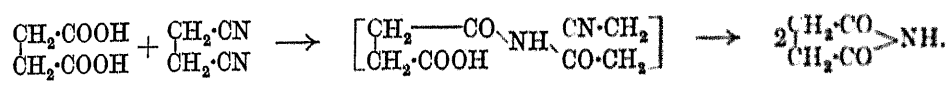


Schiller-Wechsler's synthesis of α-phenylamino-α-methyl-α-succinamic β-ester has already been mentioned (p. 50). The product is converted into the imide by the action of heat or of dilute acids or alkalies. The *o*-tolylamino-compound behaves similarly. Gault and Wieck [8] have prepared 3-phenyltriketopyrrolidine from phenylcyanopyruvic ester :

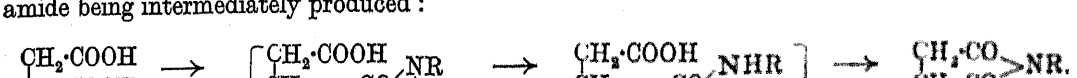


[1] Guareschi and Grande, *Zentr.*, 1899, ii, 439; Menozzi, *Gazz.*, 1900, **30**, i, 265; Ghiglieno, *Zentr.*, 1910, ii, 806, 807; Birch, Gough and Kon, *J. C. S.*, 1921, **119**, 1320.
[2] Dunlap, *Amer. Chem. J.*, 1896, **18**, 332.
[3] *Ber.*, 1913, **46**, 2563.
[4] Dunlap, *Amer. Chem. J.*, 1897, **19**, 492.
[5] *Idem, ibid.*, 1896, **18**, 332; Ruggli and Hartmann, *Helv. Chim. Acta*, 1920, **3**, 505.
[6] Bogert and Eccles, *J. A. C. S.*, 1902, **24**, 20.
[7] Bechert, *J. pr. Chem.*, 1894, **50**, 1; Passerini, *Gazz.*, 1923, **53**, i, 333.
[8] *Compt. rend.*, 1920, **170**, 1392; *Bull. Soc. chim.*, 1922, [iv], **31**, 867, 993.

(*f*) *From succinic acid and nitriles, carbimides or thiocarbimides:* König,[1] in his study of the interaction of acids and nitriles, found that succinic acid and ethylene dicyanide gave succinimide:

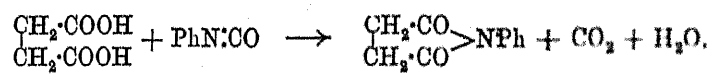


The employment of mustard oils for the conversion of succinic acid into succinimides was first described by Moiné.[2] The reaction is probably similar to that just mentioned, a secondary amide being intermediately produced:

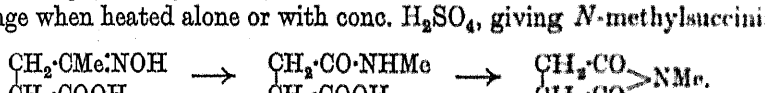


(R = allyl or phenyl.)

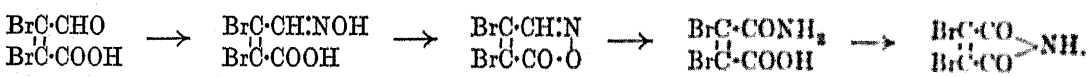
Haller[3] used phenylcarbimide in place of the thiocarbimide:



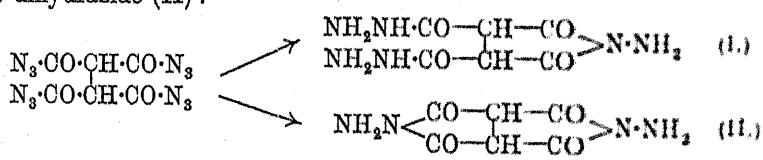
(*g*) *From oximes of γ-aldehydo- or γ-keto-acids:* The oxime of lævulic acid undergoes the Beckmann change when heated alone or with conc. H_2SO_4, giving *N*-methylsuccinimide:[4]



The oxime of mucobromic acid must first be converted into its anhydride, which then yields dibromomaleinimide when heated:[5]



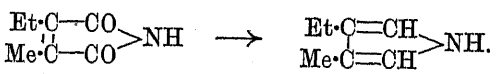
(*h*) *From acid azides:* Curtius and Thiemann[6] in their investigation of the azides of polycarboxylic acids found that the tetra-azide of ethanetetracarboxylic acid was decomposed by warm water with formation of the cyclic trihydrazide (I). Bromine water or alcoholic iodine gave the cyclic dihydrazide (II):



Reduction of succinimides, etc.: The succinimides give small yields of the corresponding pyrroles when distilled with zinc dust, but much better results are obtained by reduction with sodium and alcohol or with hydrogen in the presence of platinum black. Tafel[7] reduced

[1] *J. pr. Chem.*, 1904, **69**, 1. [2] *Jahresber.*, 1886, 558; see also P. Kay, *Ber.*, 1893, 26, 2850.
[3] *Compt. rend.*, 1892, **114**, 1326.
[4] Bredt and Böddinghaus, *Ann.*, 1889, **251**, 316; Dollfus, *Ber.*, 1892, **25**, 1930.
[5] Hill and Cornelison, *Amer. Chem. J.*, 1894, **16**, 290; Hill and Allen, *ibid.*, 1897, **19**, 658.
[6] *J. pr. Chem.*, 1916, **94**, 273–382. [7] *Ber.*, 1899, **32**, 74; 1900, **33**, 2224; 1901, **34**, 2224.

succinimide electrolytically to pyrrolidine. Grabovski and Marchlewski [1] synthesised hæmopyrrole *a* by heating methylethylmaleinimide with zinc dust and lime in an atmosphere of CO_2:



Hæmopyrrole a.

In the following list of succinimides etc. methods *e*, *f*, *g* and *h* are not included.

I. *Succinimides* have been obtained by condensation of succinic acid or anhydride with the following amines etc. (the numbers refer to the references on pp. 57, 58):

Ammonia, 1, 11, 12, 20, 56, 119, 128
Urea, 72
Methylamine, 14
Ethylamine, 14
*iso*Propylamine, 100
Allyl thiocarbimide, 29, 59
Ethylenediamine, 37, 63
Trimethylenediamine, 35
Glycine ester, 66, 140
Benzylamine, 39
Aniline, 2, 10, 12, 18, 74, 95, 108, 120, 123, 131
Phenyl carbimide, 54
Phenylthiocarbimide, 29
o-Toluidine, 16, 17, 131
p-Toluidine, 9, 13, 16, 17, 18, 74, 108
Mesidine, 22
o-Nitroaniline, 18, 74, 105
p-Nitroaniline, 18, 74, 77, 105
o-Bromo-*p*-phenetidine, 85
Anthranilic acid, 74
p-Cyanoaniline, 127
Sulphanilic acid, 36
α-Naphthylamine, 18, 36
β-Naphthylamine, 36, 74, 108
Naphthionic acid, 36
m-Phenylenediamine, 15, 105
p-Phenylenediamine, 105
Hydroxylamine, 70
Phenylhydrazine, 50

II. The following *substituted succinimides* have been prepared by normal reaction with amines:

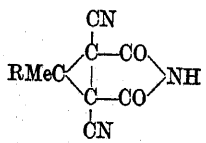
Acid or anhydride.	*Ammonia.*	*Aniline.*	p-*Toluidine.*	*β-Naphthylamine.*	*Other amines.*
MeĊH–ĊH$_2$	5, 7	6, 7, 88, 130	96	95	Methylamine, 88 Ethylamine, 88 Propylamine, 88 Benzylamine, 88
EtĊH–ĊH$_2$	—	139	—	—	—
C$_3$H$_7$ĊH–ĊH$_2$	—	124	—	—	—
CHMe$_2$ĊH–ĊH$_2$	24	71, 79, 92, 95, 106	95	95	—
COOH·CH$_2$ĊH–ĊH$_2$	—	114	—	—	—
COOR·CH:Ċ–ĊH$_2$	—	114	—	—	—
COOH·CH$_2$Ċ(OAc)–ĊH$_2$	—	114	—	—	—
OH·ĊH–ĊH$_2$	—	8	—	48	*o*-Toluidine, 48
ĊO–ĊH$_2$	—	51, 145	51	—	—
ĊO–ĊHMe	—	51	—	—	—
MeĊH–ĊHMe	38, 41, 45	38, 45, 67	67, 95	67, 95	—
EtĊH–ĊHMe	—	89, 95	89, 95	95	—
C$_3$H$_7$ĊH–ĊHMe	112	—	—	—	—
CHMe$_2$·ĊH–ĊHMe	—	71	—	—	—
CHMe$_2$CH$_2$CH$_2$ĊH–ĊHMe	—	96	—	—	—
EtĊH–ĊHEt	—	95	95	95	—
CHMe$_2$ĊH–ĊHCHMe$_2$	74	74	74	74	—
PhĊH–ĊHPh	143	—	—	—	—

[1] *Ber.*, 1914, **47**, 2159.

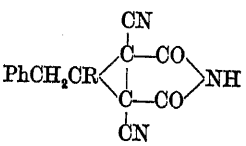
* In this and succeeding tables ·COOH groups are indicated by dots over the carbon atoms to which they are attached.

*Acid or anhydride.	Ammonia.	Aniline.	p-Toluidine.	β-Naphthylamine.	Other amines.
OHĊH–ĊHOH	—	78	—	122	Methylamine, 78, 86 Ethylamine, 78, 86 Propylamine, 78, 86 Benzylamine, 78, 86 α-Naphthylamine, 78
AcO·ĊH–ĊH·OAc	—	87, 145	87, 145	87, 145	*p*-Chloroaniline, 145 *p*-Bromoaniline, 145 2 : 4-Dichloroaniline, 145 2 : 4-Dibromoaniline, 145 *o*-Toluidine, 145 *m*-Toluidine, 145 4-*m*-Xylidine, 145
EtĊH–ĊHOH	—	110	—	—	—
BrĊH–ĊHBr	—	75	75	—	—
Me_2Ċ–ĊH$_2$	32	74, 81, 82, 90, 93	74, 82	74, 82	*o*-Toluidine, 82 α-Naphthylamine, 82 Phenylhydrazine, 32
EtMeĊ–ĊH$_2$	—	89	74, 89	89	—
Me_2Ċ–ĊHMe	68	65, 67	67	67	—
Me_2Ċ–ĊMe_2	49	49, 74	74	74	Benzidine, 74 Phenylhydrazine, 74
(COOEt)$_2$Ċ–Ċ(COOEt)$_2$	136	—	—	—	—

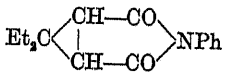
III. The following *alicyclic succinimides* are known :



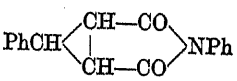
R = methyl (94, 137)
ethyl (94, 125)
propyl (97)
*iso*propyl (97)
hexyl (94)
benzyl (132)



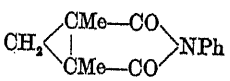
R = methyl (132)
ethyl (132)
*iso*propyl (132)



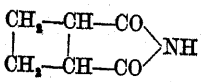
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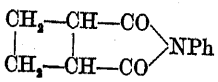
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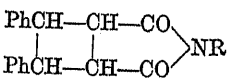
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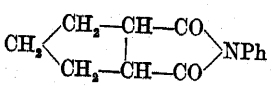
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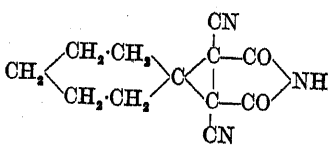
(58, 61)



R = Ph, ·NHPh (57)



(61)



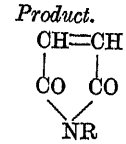
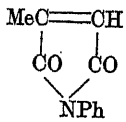
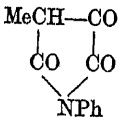
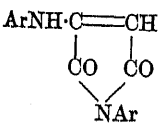
(137)

* See footnote on p. 53.

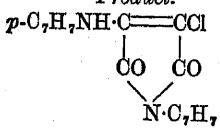
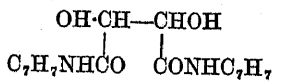
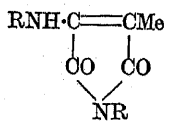
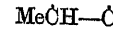
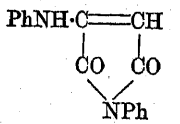
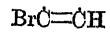
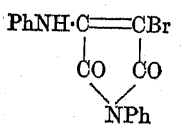
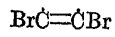
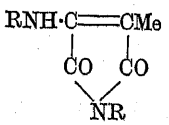
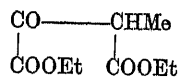
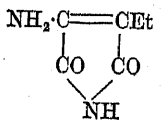
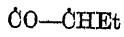
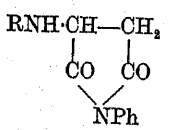
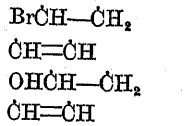
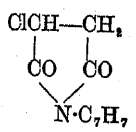
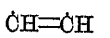
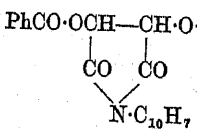
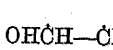
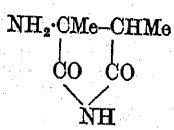
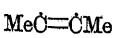
IV. *Maleinimides* have been obtained directly *from maleic acids* as follows :

*Acid or anhydride.	Ammonia.	Aniline.	Other amines.
ĊH=ĊH	3	19, 27	Urea (fails), 83 Methylamine, 47, 73 Ethylamine, 73 Benzylamine, 73 Hydrazine, 64
MeĊ=ĊH	4, 23	4, 27, 43	*o*-Toluidine, 116 *p*-Toluidine, 34 *m*-Aminobenzoic acid, 34 *p*-Aminodimethylaniline, 34 Phenylhydrazine, 34 Halogenated phenylhydrazines, 138 *o*-, *p*-Tolylhydrazines, 136
EtĊ=ĊH	—	110	—
BrĊ=ĊH	—	27	—
BrĊ=ĊMe	—	27, 34	*p*-Aminodimethylaniline, 116
ClĊ=ĊCl	—	80	Urea, 72
BrĊ=ĊBr	—	—	Urea, 73, 133
MeĊ=ĊMe	21, 26, 99, 118, 133	26	—
EtĊ=ĊMe	52, 115	109	—
EtĊ=ĊEt	117, 121	—	—
C_3H_7Ċ=ĊMe	111, 113, 117	—	—
$CHMe_2$·Ċ=ĊMe	117	—	—
$CHMe_2$·CH_2CH_2Ċ=ĊMe	96	—	—
COOH·CH_2CH_2Ċ=ĊMe	101	—	—
PhĊ=ĊPh	—	—	*o*-Phenylenediamine, 144

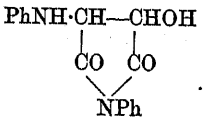
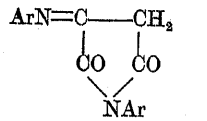
V. The following *maleinimides*, *aminomaleinimides* and *aminosuccinimides* have been prepared by indirect methods :

Product.	Prepared from: * Acid or anhydride etc.	Amine etc.		References.
	OH·ĊH—ĊH$_2$	R·NH$_2$	R = methyl ethyl benzyl phenyl	53 33 53 31
	PhNH·ĊMe—ĊH$_2$	(heated)		28, 46
	COOH·CH_2Ċ(OH)·ĊH$_2$ PhNH·ĊO ĊONHPh	(heated)		114
	COOEt ĊOOEt	Propionanilide		51
	COOEt ĊOOEt	Acetanilide Aceto-*p*-toluidide		51 51
	BrĊH—ĊHBr CO———CH_2 ĊOOEt ĊOOEt	Aniline Aniline		44 28
	OH·ĊH—ĊHOH PhNHĊO ĊONHPh	(+ PCl_5)		60

* See footnote on p. 53.

Product.	*Prepared from* * *Acid or anhydride etc.*	*Amine etc.*		*References.*
		(+ PCl_5)		60
		R·NH_2	R = phenyl	116
			o-tolyl	116
			p-tolyl	103, 104, 116
			p-NMe_2·C_6H_4.	116
		Aniline		27, 34
		Aniline		34
		R·NH_2	R = hydrogen	91
			phenyl	44
		Ammonia		91
		Ammonia		30, 33, 76
		Aniline		42
		Aniline		122
		Aniline		122
		Aniline (+ PCl_5)		60
		*p*-Toluidine (+ PCl_5)		60
		α- and β-Naphthylamines (+ benzoyl chloride)		60
		Ammonia		99

* See footnote on p. 53.

Product.	*Prepared from* * *Acid or anhydride etc.*	*Amine etc.*	*References.*
	Cl·ĊH—ĊHOH	Aniline	135
	AcO·ĊH—ĊH·OAc	Aniline	87, 145
		p-Chloroaniline	145
		p-Bromoaniline	145
		m-Toluidine	145
		p-Toluidine	87, 145
		β-Naphthylamine	87

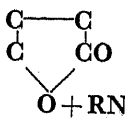
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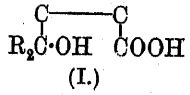
* See footnote on p. 53.

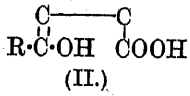
163; 1900, **16**, 156. [97] Menozzi, *Gazz.*, 1900, **30**, i, 265. [98] Paolini, *ibid.*, ii, p. 505. [99] Molinari, *Ber.*, 1900, **33**, 1412. [100] Tafel and Stern, *ibid.*, p. 2232. [101] Küster, *ibid.*, p. 3022. [102] Bogert and Eccles, *J. A. C. S.*, 1902, **24**, 20. [103] Enzenauer, *Dissn. Basle*, 1900. [104] Fichter and Preiswerk, *Ber.*, 1902, **35**, 1626. [105] R. Meyer, *Ann.*, 1903, **327**, 18, 24, 27, 31, 39, 46–49. [106] Semmler, *Ber.*, 1903, **36**, 1749. [107] König, *J. pr. Chem.*, 1904, **69**, 1. [108] Koller, *Ber.*, 1904, **37**, 1598. [109] Fichter and Rudin, *ibid.*, p. 1617. [110] Fichter and Goldhaber, *ibid.*, p. 2382. [111] Küster and Haas, *ibid.*, p. 2471. [112] Tschugaev and Schlœsinger, *Zentr.*, 1905, i, 536. [113] Buraczewski and Marchlewski, *Zeitschr. physiol. Chem.*, 1905, **43**, 410. [114] Bertram, *Ber.*, 1905, **38**, 1615. [115] Küster and Haas, *Ann.*, 1906, **345**, 18. [116] Fichter and Tschudin, *J. pr. Chem.*, 1906, **74**, 297. [117] Küster and Haas, *Ann.*, 1906, **346**, 19. [118] Rossi, *Gazz.*, 1906, **36**, ii, 860. [119] de Mouilpied and Rule, *J. C. S.*, 1907, **91**, 178. [120] Tingle and Cram, *Amer. Chem. J.*, 1907, **37**, 596. [121] Küster and Fuchs, *Zeitschr. physiol. Chem.*, 1908, **55**, 505. [122] Tingle and Bates, *J. A. C. S.*, 1909, **31**, 1233. [123] Komatsu, *Zentr.*, 1909, ii, 983. [124] Locquin, *Bull.*, 1909, [iv], **5**, 1071. [125] Ghiglieno, *Zentr.*, 1910, ii, 806–807. [126] Barbier and Locquin, *Compt. rend.*, 1911, **153**, 188. [127] Bogert and Wise, *J. A. C. S.*, 1912, **34**, 693. [128] Rooder, *Ber.*, 1913, **46**, 2563. [129] Locquin, *Bull.*, 1914, [iv], **15**, 747. [130] Morrell, *J. C. S.*, 1914, **105**, 2704. [131] Ruggli, *Ann.*, 1917, **412**, 13. [132] Guareschi, *Gazz.*, 1918, **48**, ii, 83–98. [133] Ruggli and Hartmann, *Helv. Chim. Acta*, 1920, **3**, 505. [134] Gault and Wieck, *Compt. rend.*, 1920, **170**, 1392. [135] Dakin, *J. Biol. Chem.*, 1921, **48**, 273. [136] Philippi, Hanusch and v. Wacek, *Ber.*, 1921, **54**, 895. [137] Birch, Gough and Kon, *J. C. S.*, 1921, **119**, 1320, 1324. [138] Chattaway and Parkes, *ibid.*, 1922, **121**, 285–287. [139] Carrière, *Ann. chim.*, 1922, [ix], **17**, 38–132. [140] Curtius and Hechtenberg, *J. pr. Chem.*, 1922, **105**, 302. [141] Deshapande and Thorpe, *J. C. S.*, 1922, **121**, 1438. [142] Gault and Wieck, *Bull.*, 1922, [iv], **31**, 867, 993. [143] Lapworth and McCrae, *J. C. S.*, 1922, **121**, 1712. [144] Bistrzycki and Fässler, *Helv. Chim. Acta*, 1923, **6**, 521. [145] Chattaway and Parkes, *J. C. S.*, 1923, **123**, 663.

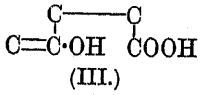
7. From γ-lactones and amines:

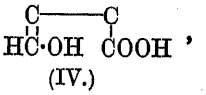


From a study of the behaviour of fifty-one lactones (β-, γ-, and δ-) towards ammonia, H. Meyer [1] has deduced the following rules. The formation of lactam or of hydroxy-amide depends only upon the nature of the ·OH group in the hydrolysed lactone. If this is tertiary (I, II, III),

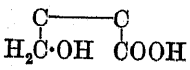

(I.)

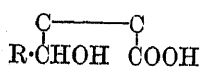

(II.)

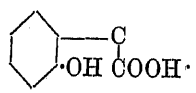

(III.)


(IV.)

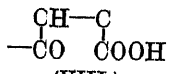
the lactam is formed, as also when the ·OH is secondary but adjoins an ethylene linkage (IV). On the other hand, the product is a hydroxy-amide if the ·OH is primary (V) or secondary (without the adjacent double bond) (VI) or phenolic (VII):

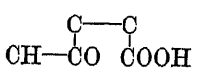

(V.)

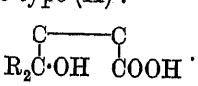

(VI.)


(VII.)

It will thus be seen that the pyrrole ring will only be formed in the case of lactones derived from enolisable γ-keto-acids (VIII and IX) or from γ-hydroxy-acids of the type (X):


(VIII.)

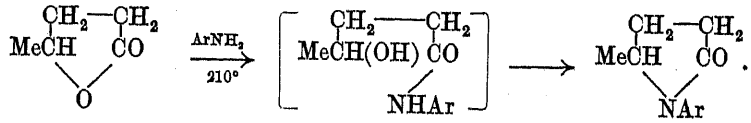

(IX.)


(X.)

These rules apply only to reactions carried out at moderate temperatures.

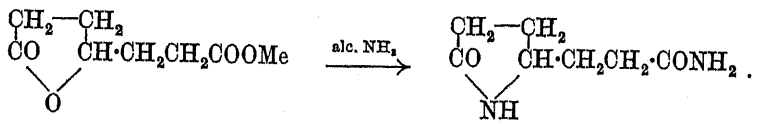
[1] *Monatsh.*, 1899, **20**, 717–733.

Emmert and E. Meyer [1] have prepared pyrrolidones by heating valerolactone at 210° with a mixture of an arylamine and its hydrochloride :

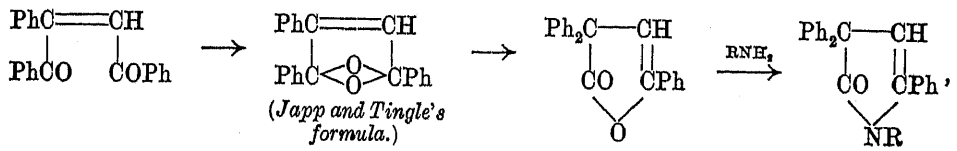


(Ar = Ph, *o*-, *p*-C_7H_7·, *m*-NO_2·C_6H_4·.)

A more complex valerolactone was converted into the corresponding pyrrolidone by Leuchs and Nagel : [2]



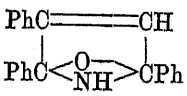
Triphenylpyrrolones have been obtained by Japp [3] from dibenzoylstyrene by the action of ammonia or amines. The dibenzoylstyrene is apparently first isomerised to triphenylcrotolactone, which then reacts normally :



(*Japp and Tingle's formula.*)

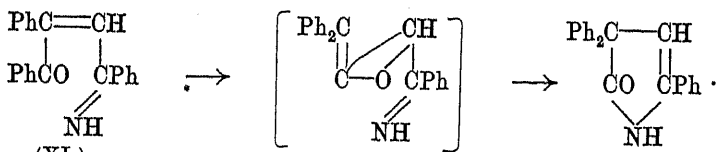
(R = H, Me, Et, ·C_3H_7, ·C_3H_5, ·NHPh.)

Japp and Tingle [4] were able to isolate a compound



(m.p. 180°)

which readily isomerised to the triphenylpyrrolone when warmed at its melting point. The same compound was obtained by Oliveri-Mandalà and Calderaro [5] by the action of light upon dibenzoylstyrene dissolved in alcoholic ammonia. They consider, however, that it has the structure (XI), and its conversion into triphenylpyrrolone is figured thus :

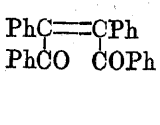


(XI.)

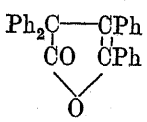
In the absence of further evidence the lactone explanation seems preferable.

[1] *Ber.*, 1921, **54**, 210.
[2] *Ibid.*, 1922, **55**, 3954.
[3] Japp and Klingemann, *J. C. S.*, 1890, **57**, 691, 708; Japp and Tingle, *ibid.*, 1897, **71**, 1138.
[4] *Loc. cit.*
[5] *Gazz.*, 1914, **44**, ii, 85.

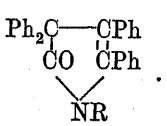
From dibenzoylstilbene (XII) and from the isomeric tetraphenylcrotolactone (XIII) Klingemann and Laycock [1] prepared the corresponding pyrrolones (XIV) by the action of alcoholic ammonia or methylamine at 200° :



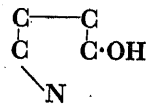
(XII.)



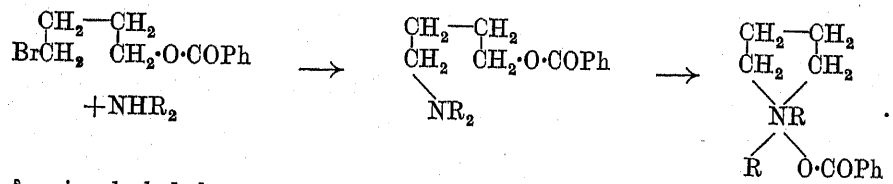
(XIII.)



(R = H, Me.)
(XIV.)

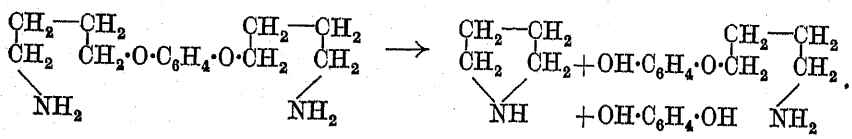
8. From δ-aminoalcohols or γ-hydroxy-amides : 

v. Braun [2] has prepared a series of ω-aminoalkyl benzoates. Those which contain a four- or five-carbon chain undergo rearrangement, either at the moment of formation or on distillation, giving cyclic quaternary salts :

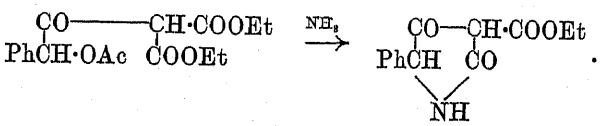


The free δ-aminoalcohols have not been prepared.

Wilson and Adams [3] heated the monohydrochloride of resorcinol *bis*-δ-aminobutyl ether in the hope of obtaining a thirteen-membered ring; the products, however, were resorcinol, the mono-ether and pyrrolidine :

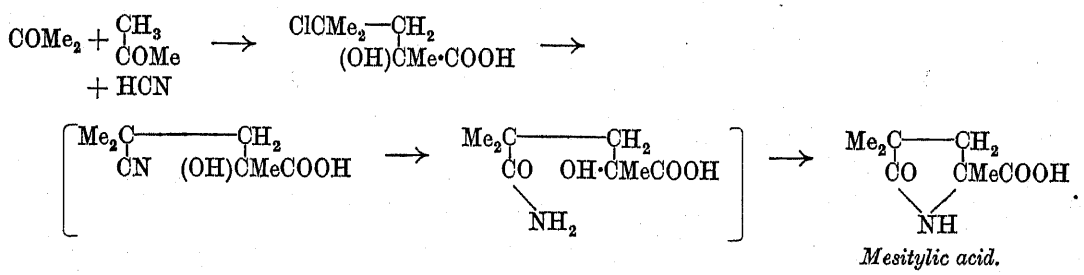


γ-Hydroxyamides seem to be equally incapable of existence unless the ·NH_2 group is fully substituted. Anschütz [4] obtained a diketopyrrolidine by the action of ammonia upon acetoxyphenylacetylmalonic ester :



[1] *J. C. S.*, 1891, **59**, 142.
[2] *Ber.*, 1916, **49**, 966.
[3] *J. A. C. S.*, 1923, **45**, 528.
[4] *Ann.*, 1909, **268**, 53.

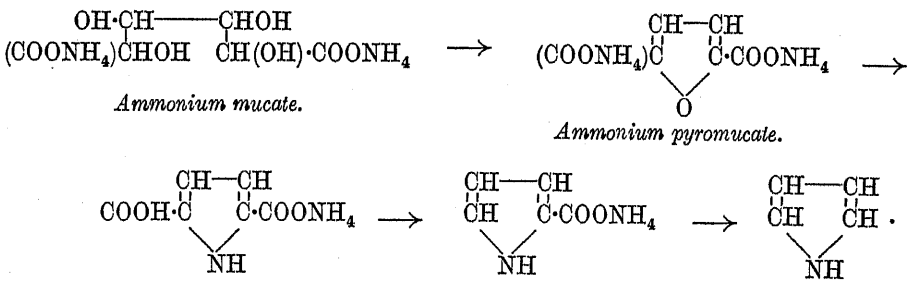
Mesitylic acid, the product obtained by treating with alcoholic KCN a mixture of acetone and HCl which has been allowed to stand for eight days [1] was shown by Pinner [2] to be a pyrrolidone derivative :



Mesitylic acid.

9. From mucic acid : $\begin{matrix}C{-}C\\ OH{\cdot}C\quad C{\cdot}OH\end{matrix}$ + NH_2R

By distillation of ammonium mucate, pyrroledicarboxylic acid and eventually pyrrole itself is obtained.[3] The conditions for the best yield (42%) of pyrrole have been worked out by Khotinsky : [4]



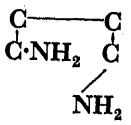
Ammonium mucate.

Ammonium pyromucate.

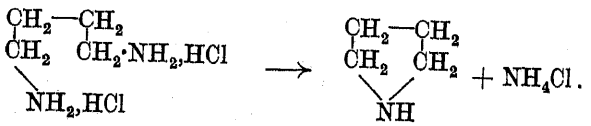
Distillation of mucic acid with primary amines gives in the same way *N*-substituted pyrroles. Methyl-, ethyl- and amyl-pyrroles were so obtained by Bell; [5] phenylpyrrole by Köttnitz,[6] and the *p*-tolyl derivative by Lichtenstein.[7] α-Aminopyridine and mucic acid must be heated to 255° with Al_2O_3 in order to give *N*-α-pyridylpyrrole.[8]

Saccharic acid gives the same products as mucic acid.[9]

[1] Simpson, *Proc. Roy. Soc.*, 1868, **16**, 364; *Ann.*, 1868, **148**, 351.
[2] *Ber.*, 1881, **14**, 1070; 1882, **15**, 576.
[3] Schwanert, *Ann.*, 1860, **116**, 257.
[4] *Ber.*, 1909, **49**, 2506.
[5] *Ibid.*, 1876, **9**, 936; 1877, **10**, 1861; *Proc. Roy. Irish Acad.*, 1877, [ii], **3**, 33.
[6] *J. pr. Chem.*, 1873, **6**, 136; see also Lichtenstein, *Ber.*, 1881, **14**, 933; Pictet and Steinmann, *ibid.*, 1902, **35**, 2529; Feist, *ibid.*, p. 1654 footnote.
[7] *Loc. cit.*
[8] Tschitschibabin and Bylinkin, *ibid.*, 1923, **56**, 1745; Wibaut and Dingemanse, *Rec. trav. chim.*, 1923, **42**, 1039.
[9] Bell and Lapper, *Ber.*, 1877, **10**, 1961; Altmann, *Dissn. Neisse*, 1874.

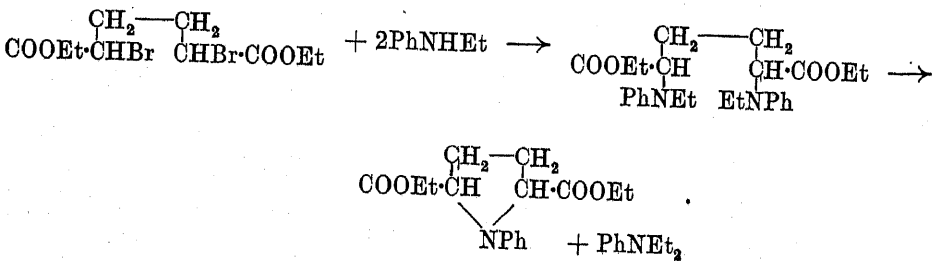
10. From 1:4-diamines: 

Tetramethylenediamine hydrochloride and its derivatives are easily converted into pyrrolidines by dry distillation:[1]



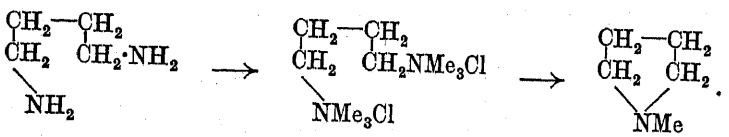
β-Methylpyrrolidine was similarly prepared by Oldach.[2]

The ease with which the pyrrolidine ring-closure takes place is illustrated in the remarkable example observed by Le Sueur:[3]

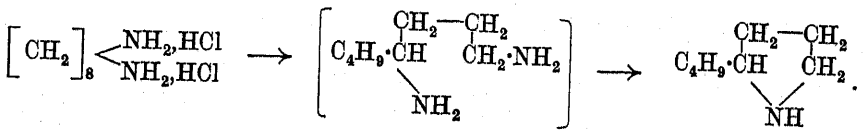


The yield is 62% and no ethyl bromide is formed.

Tetramethylenediamine was fully methylated by Willstätter and Hübner,[4] who obtained 1-methylpyrrolidine by distillation of the product with alkali:

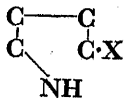


Blaise and Houillon[5] supposed that they had obtained 2-butylpyrrolidine by the distillation of octamethylenediamine hydrochloride:



Hess[6] has shown, however, that the product has not this structure. The side-chain is perhaps an *iso*butyl group.

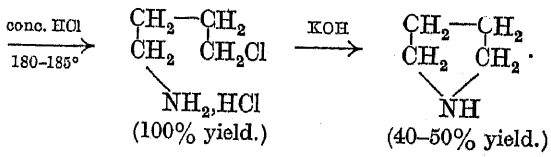
[1] Ladenburg, *Ber.*, 1886, **19**, 782; 1887, **20**, 442; Petersen, *ibid.*, 1888, **21**, 290.
[2] *Ibid.*, 1887, **20**, 1654.
[3] *J. C. S.*, 1909, **95**, 273; 1910, **97**, 173.
[4] *Ber.*, 1907, **40**, 3873.
[5] *Compt. rend.*, 1906, **142**, 1531; **143**, 361.
[6] *Ber.*, 1919, **52**, 1636.

11. From δ-halogenated amines: 

Aliphatic bases containing $\cdot NH_2$ and halogen in the 1 : 4-position exist only in the form of their salts. On liberation of the base it at once condenses to a pyrrole derivative.[1] For this synthesis the phthalimide method may be used, or the halogen may be introduced by the hydrolysis of a suitable phenoxy-compound:

$$ClCH_2CH_2CH_2\cdot CN \xrightarrow{NaOPh} PhO\cdot CH_2CH_2CH_2\cdot CN \xrightarrow{Na+alc.} PhO\cdot CH_2CH_2CH_2CH_2NH_2$$

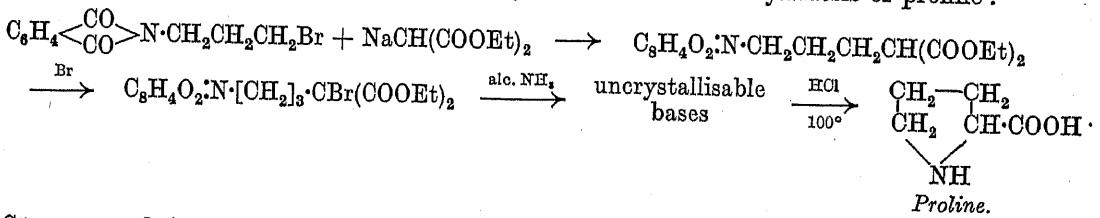
(80% yield.) (75% yield.)



(100% yield.) (40–50% yield.)

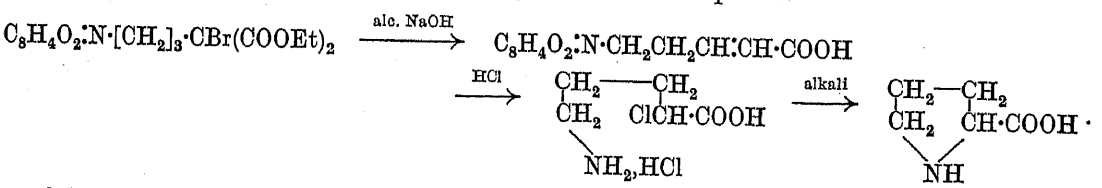
v. Braun and Beschke [2] obtained a much greater yield (83%) by using fuming HBr in place of conc. HCl and isolating the product as benzoyl derivative. The method thus modified is suitable for the preparation of large quantities of pyrrolidine.[3]

The phthalimide method was employed by E. Fischer [4] in his synthesis of proline:

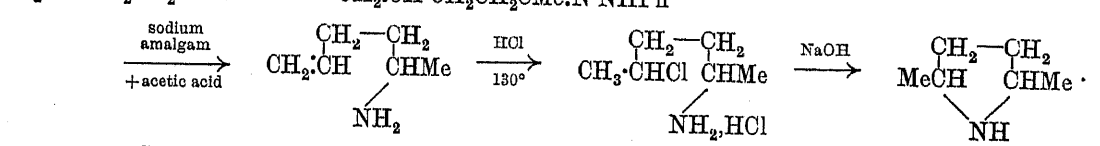


Proline.

Sörensen and Andersen [5] substituted alcoholic NaOH for the alcoholic NH_3 and obtained an unsaturated phthalimino-acid which was easily converted into proline:

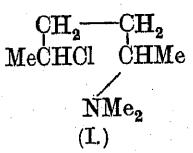


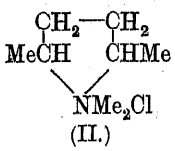
Other examples of the introduction of a δ-chlorine atom by addition of HCl at a double linkage have been recorded by Merling: [6]

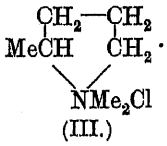


[1] Gabriel, *Ber.*, 1891, **24**, 3233.
[2] *Ibid.*, 1906, **39**, 4120.
[3] See, further, Putochin, *ibid.*, 1922, **55**, 2742.
[4] *Ibid.*, 1901, **34**, 454.
[5] *Z. physiol. Chem.*, 1908, **56**, 236.
[6] *Ann.*, 1891, **264**, 317, 327, 332.

Ring-closure even occurs in the case of the corresponding tertiary amine (I), the product being a pyrrolidinium chloride (II):

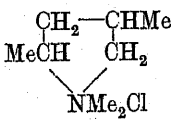

(I.)

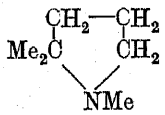

(II.)

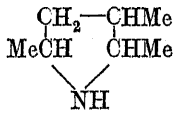

(III.)

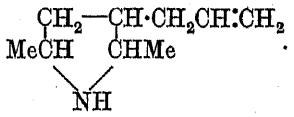
From $CH_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$, the product of the exhaustive methylation of piperidine, Merling in the same way obtained the compound (III). No ring-closure occurred, however, with the unsaturated base from α-pipecoline, $CH_2{:}CH{\cdot}CH_2CH_2CHMe{\cdot}NMe_2$; the methyl group adjacent to the $\cdot NMe_2$ appears to exercise steric hindrance.

Jacobi and Merling [1] have described similar syntheses leading to the following pyrrolidines:

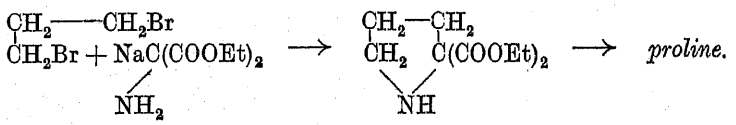




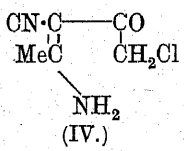


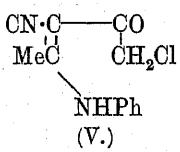


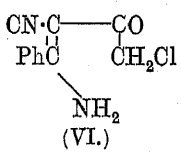
The new proline synthesis [2] makes use of aminomalonic ester for the preparation of the δ-amino-halide:

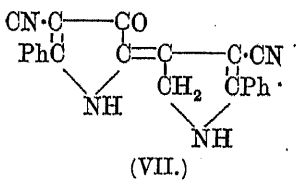


Some anomalous cases are described by Benary and Lau,[3] who find that α-chloroacetyl-β-aminocrotonitrile (IV) cannot be converted into the pyrrolone. The corresponding anilino-nitrile (V) requires aqueous-alcoholic KOH, while α-chloroacetyl-β-aminocinnamic nitrile (VI) yields with KOH a bimolecular product (VII):

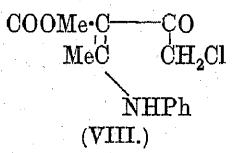

(IV.)

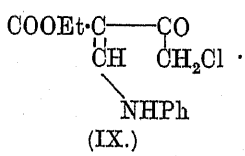

(V.)


(VI.)


(VII.)

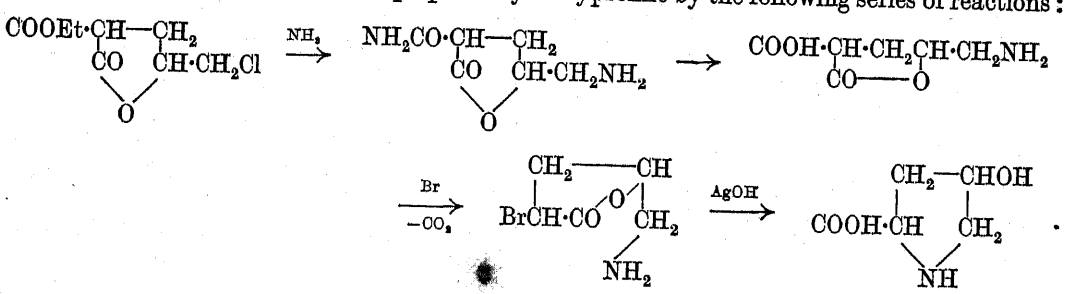
The methyl ester (VIII) corresponding to (V) and also the simpler ester (IX) give pyrrolones when treated with alcoholic KOH: [4]


(VIII.)


(IX.)

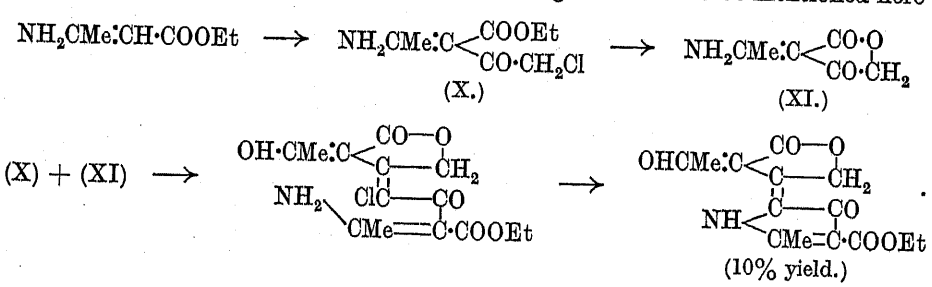
[1] *Ann.*, 1894, **278**, 8, 10, 13, 16.
[2] Putochin, *Ber.*, 1923, **56**, 2213.
[3] *Ibid.*, pp. 591–597.
[4] Benary and Konrad, *ibid.*, pp. 47, 50.

Traube, Johow and Tepohl [1] have prepared hydroxyproline by the following series of reactions:



Hydroxyproline.

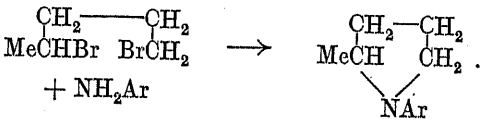
The complex pyrrolone obtained by Küster and Maag [2] should also be mentioned here:



(10% yield.)

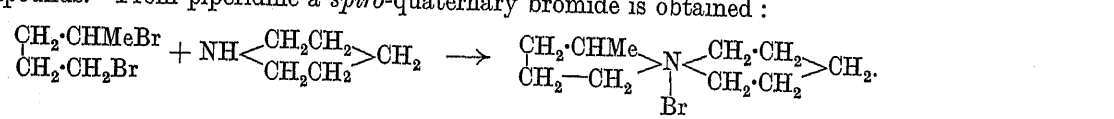
12. From α:δ-dihalides: $\begin{matrix} C\text{—}C \\ X\cdot C \quad C\cdot X \end{matrix}$ + NH_2R

This is a natural extension of the foregoing method. Scholtz and Friemelt [3] condensed α:δ-dibromopentane with a number of aromatic primary amines and obtained, except in the case of ortho-substituted arylamines, the corresponding pyrrolidines:



(Ar = Ph, *p*-C_7H_7·, *m*-$NO_2\cdot C_6H_4$.)

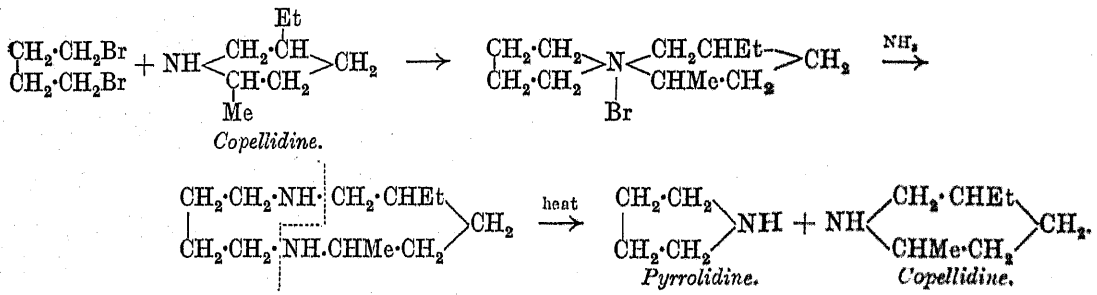
o-Toluidine and *o*-nitroaniline, as with xylylene dibromide (see p. 150), give diamines but no ring-compounds. From piperidine a *spiro*-quaternary bromide is obtained:



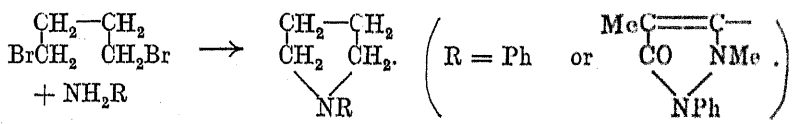
A similar *spiro*-compound results from the condensation of tetramethylene dibromide and

[1] *Ber.*, 1923, **56**, 1861. [2] *Ibid.*, p. 61. [3] *Ibid.*, 1899, **32**, 848.

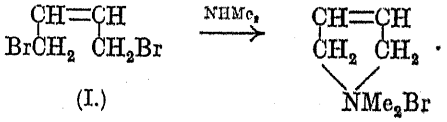
copellidine.[1] From this, pyrrolidine is conveniently obtained by treatment with ammonia followed by distillation :



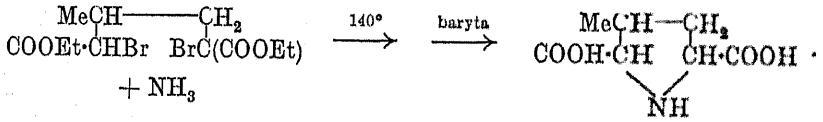
Quantitative yields of *N*-phenyl- and *N*-antipyrinyl-pyrrolidines have been obtained by v. Braun and Lemke [2] from tetramethylene dibromide :



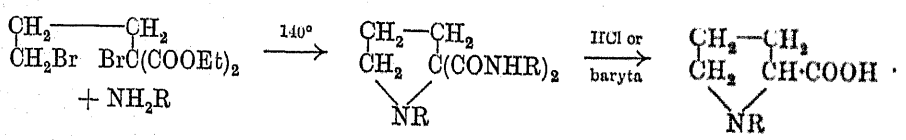
The unsaturated $\alpha:\delta$-dibromo-Δ^{β}-butene (I) gives much smaller yields (40%) in these cases. With dimethylamine, it gives a small amount of the methobromide of 1-methyl-2 : 5-dihydropyrrole :



Willstätter and v. Sicherer [3] prepared 3-methylpyrrolidine-2 : 5-dicarboxylic acid by heating $\alpha:\alpha'$-dibromo-β-methyladipic ester with methyl-alcoholic ammonia at 140°, the resulting amides being hydrolysed with baryta :



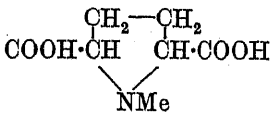
The reaction was applied by Willstätter [4] to the synthesis of proline and of hygric acid from $\alpha:\delta$-dibromopropylmalonic ester :



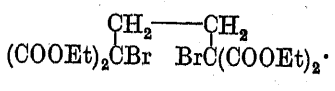
(R = H for proline, Me for hygric acid.)

[1] v. Braun, Lemke and Nelken, *Ber.*, 1923, **56**, 1564.
[2] *Ibid.*, 1922, **55**, 3556.
[3] *Ibid.*, 1899, **32**, 1291.
[4] *Ibid.*, 1900, **33**, 1164; Willstätter and Ettlinger, *ibid.*, 1902, **35**, 620; *Ann.*, 1903, **326**, 91.

α : α′-Dibromoadipic ester reacts similarly with methylamine in benzene at 135°, and an 80% yield of 1-methylpyrrolidine-2 : 5-dicarboxylic acid (II) is obtained on hydrolysis. The corresponding tetracarboxylic ester (III) reacts much less smoothly : [1]

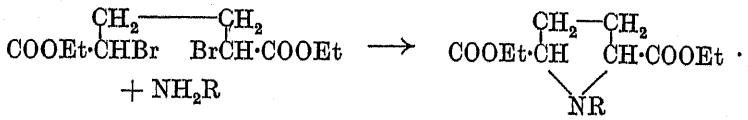


(II.)



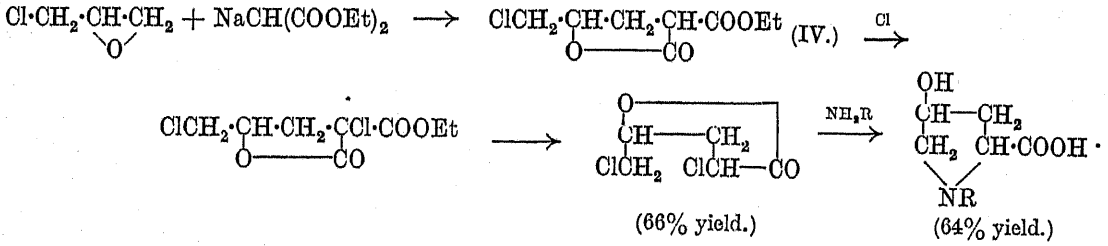
(III.)

α : α′-Dibromoadipic ester has recently been used by v. Braun and Seemann [2] for the preparation of *N*-substituted pyrrolidines required for the synthesis of morphopyrrolidines :



(R = Me, ·CH_2Ph, Ph.)

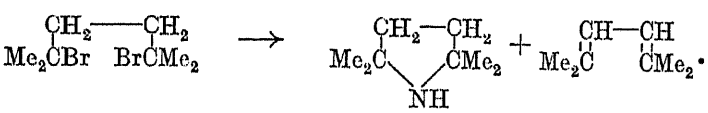
The δ-chlorovalerolactone-α-carboxylic ester (IV) obtained from epichlorohydrin and sodiomalonic ester,[3] has been used by Leuchs [4] for the preparation of hydroxyproline and its *N*-methyl derivative :



(66% yield.) (64% yield.)

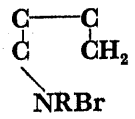
(R = H, Me.)

The compound $BrCMe_2·CH_2·CH_2·CMe_2Br$ gives very little tetramethylpyrrolidine (V) when treated with alcoholic NH_3 at 100°, the main product being tetramethylbutadiene (VI) : [5]

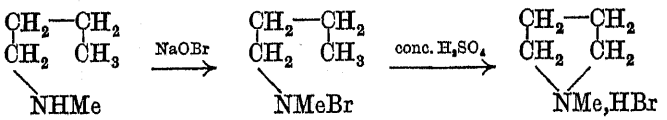


(Little.) (V.) (Main product.) (VI.)

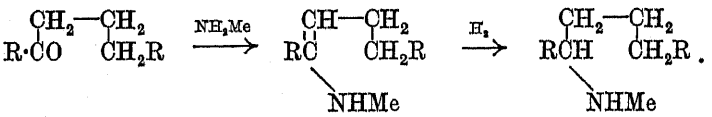
[1] Willstätter and Lessing, *Ber.*, 1902, **35**, 2067, 2071.
[2] *Ibid.*, 1923, **56**, 1840.
[3] Traube and Lehmann, *ibid.*, 1899, **32**, 720; 1901, **34**, 1971.
[4] *Ibid.*, 1905, **38**, 1937; Leuchs, Giua and Brewster, *ibid.*, 1912, **45**, 1960; Leuchs and Bormann, *ibid.*, 1919, **52**, 2090; Leuchs and Felser, *ibid.*, 1908, **41**, 1732.
[5] Pauly and Hültenschmidt, *ibid.*, 1903, **36**, 3357, footnote.

13. From the bromyl derivatives of butylamines : 

In this synthesis, which is due to Löffler,[1] bromine is introduced into a secondary amino group and the ring is closed by treatment with conc. H_2SO_4 :

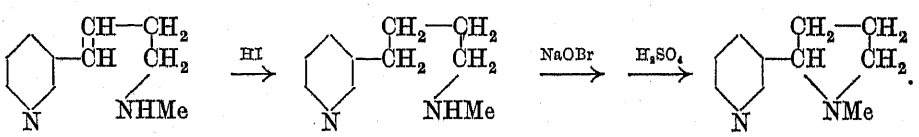


The methylalkylamines are conveniently prepared by the reduction, with sodium and alcohol, of the product obtained by the action of methylamine upon the appropriate ketone :



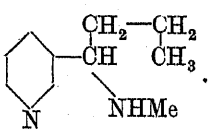
Dipropyl, ethyl propyl and methyl propyl ketones, and also *iso*butyraldehyde, have in this way been converted into pyrrolidines. The reaction failed in the case of *normal* amylmethylamine, neither a pyrrolidine nor a piperidine being formed.

Löffler and Kober [2] used this method in the partial synthesis of nicotine from metanicotine :



"*Metanicotine.*" *Nicotine.*

Attempts to prepare 3-β-methylaminobutylpyridine (I) for a new complete synthesis of nicotine were unsuccessful :



(I.)

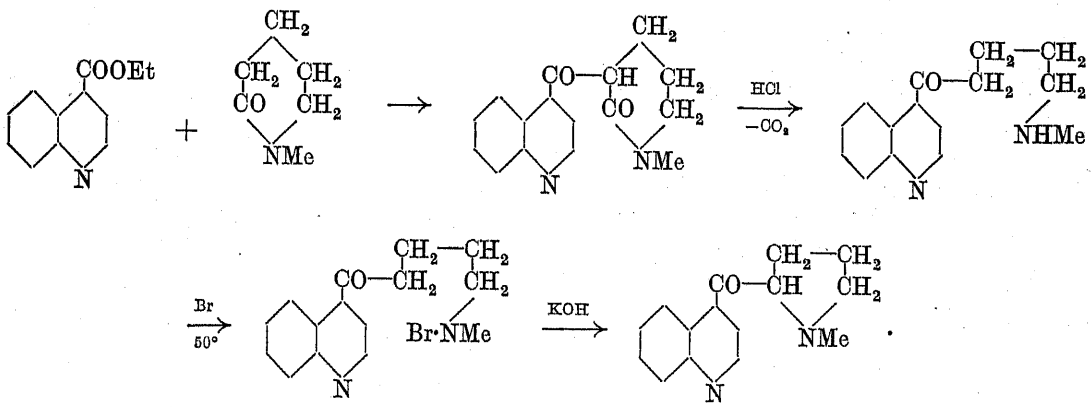
A further interesting application of Löffler's method is described by Ruzicka,[3] who

[1] Löffler and Freytag, *Ber.*, 1909, **42**, 3427; Löffler, Freytag, Lukowsky and Bobilov, *ibid.*, 1910, **43**, 2035–2047.

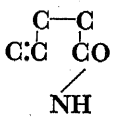
[2] *Ibid.*, 1909, **42**, 3434.

[3] *Helv. Chim. Acta*, 1921, **4**, 491.

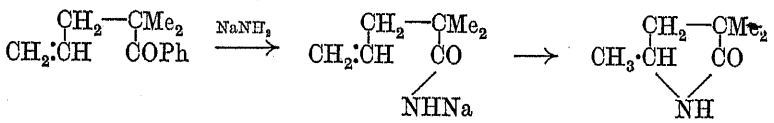
employed it for the cyclisation of 4 : δ-methylamino-*n*-valeroylquinoline, a synthetic aliphatic quinatoxine :



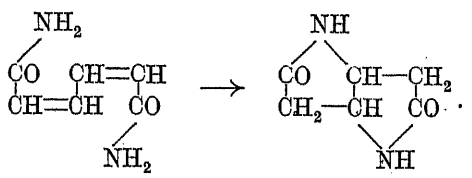
14. From γ : δ-unsaturated amides :



Allyl*iso*butyrophenone was found by Haller and Bauer [1] to react with sodamide to form 2 : 4 : 4-trimethyl-5-pyrrolidone. The phenyl group is first displaced by ·NHNa, and ring-closure follows by addition at the double bond of the allyl group :

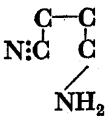


A similar ring-closure occurs when the amide of muconic acid is heated with ammonia [2] :

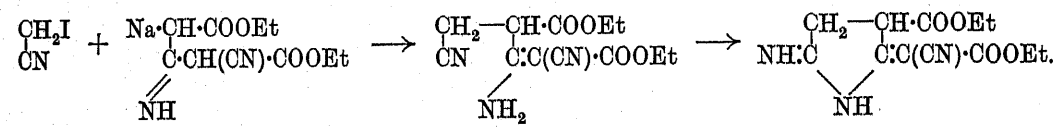


[1] *Ann. Chim.*, 1913, [viii], **28**, 373; *Compt. rend.*, 1914, **158**, 1086. [2] Köhl, *Ber.*, 1903, **36**, 172.

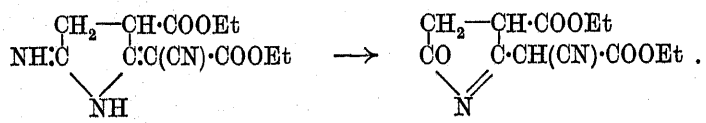
15. From γ-aminonitriles:



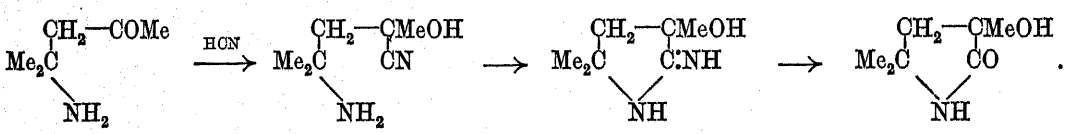
The dimeride of cyanacetic ester condenses with iodoacetonitrile in the presence of NaOEt to form a γ-aminonitrile, which under the conditions of the reaction undergoes isomerisation at once to a pyrrole derivative: [1]



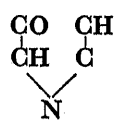
When the imino-group is removed by hydrolysis, the compound assumes the pyrrolenone form:



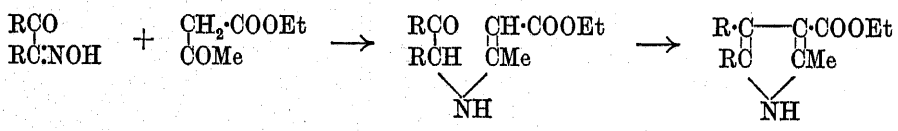
A similar intramolecular condensation between ·NH_2 and ·CN groups probably occurs when diacetonamine hydrochloride is treated with KCN: [2]



16. From α-aminoketones and β-ketoesters, etc.:



This very general synthesis is due to Knorr,[3] who reduced *iso*nitrosoketones in the presence of acetoacetic ester with zinc and acetic acid:

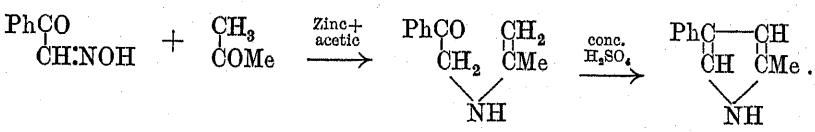


The *iso*nitroso-body is reduced first to aminoketone, which at once condenses with the keto-ester to give an aminocrotonic ester. This loses water and the pyrrole is formed.

[1] Best and Thorpe, *J. C. S.*, 1909, **95**, 1506; 1910, **97**, 1299.
[2] Heintz, *Ann.*, 1877, **189**, 231; Weil, *ibid.*, 1886, **232**, 209.
[3] *Ber.*, 1884, **17**, 1638; *Ann.*, 1886, **236**, 317.

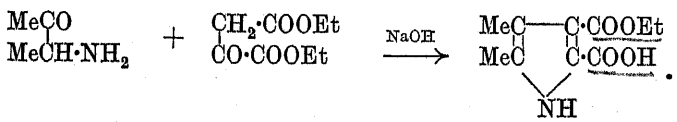
A careful investigation of the reaction by Knorr and Lange [1] showed that better yields were obtained in all cases when the aminoketone was separately prepared and condensed with a β-keto-ester or β-diketone in the presence of acetic acid. Thus acetoacetic ester with *iso*nitroso-acetophenone gives a 56% yield, compared with 100% from aminoacetophenone. Benzoyl-acetone gives only 4·5% yield with *iso*nitrosoacetophenone, but 38% with the aminoketone. The reaction fails in both cases with oxalacetic ester, acetylpyruvic ester, dibenzoylmethanes, formylacetone, phenylacetone, diphenylacetone, phenylglyoxal and desoxybenzoin.

From acetone and *iso*nitrosoacetophenone (or aminoacetophenone) the intermediate phenacyl*iso*propenylamine is obtained, and this must be treated with conc. H_2SO_4 in order to convert it into the pyrrole :



The same behaviour is observed when *iso*nitrosoacetone is reduced in the presence of acetone or of methyl ethyl ketone.

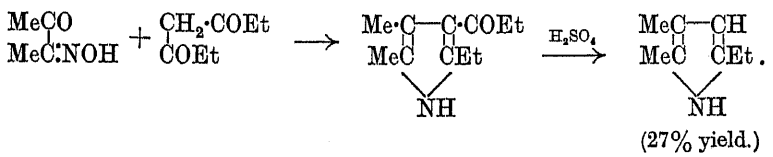
The use of alkali in place of acid for the condensation of α-aminoketones with β-keto-esters was introduced by Piloty.[2] This modification enables the method to be applied to oxalacetic and acetylpyruvic esters. Thus aminobutanone and oxalacetic ester in the presence of NaOH give a pyrrole unobtainable by Knorr's method : [3]



The α-carbethoxy-group is always hydrolysed to ·COOH when NaOH is employed as condensing agent.

The condensation, even with acetoacetic ester, occurs only slowly in alkaline solution. Amino-acetone and acetoacetic ester gave a 25% yield after several days; aminoacetone and acetone yielded 50% of 2 : 3 : 5-trimethylpyrrole in two months.

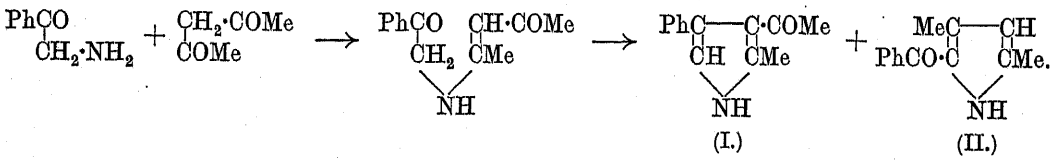
The β-acylpyrroles obtained by Knorr and Piloty's methods readily lose the acyl group on hydrolysis with sulphuric acid. For the synthesis of pyrroles having a free β-position it is unnecessary, therefore, to use methyl ketones of the type $MeCO{\cdot}CH_2R$ (which give poor yields and a mixture of two isomerides); a symmetrical diketone, $RCO{\cdot}CH_2{\cdot}CO{\cdot}R$, is employed and the β-acyl group afterwards eliminated. In this way H. Fischer and Bartholomäus [4] synthesised 2 : 3-dimethyl-5-ethylpyrrole from *iso*nitrosobutanone and dipropionylmethane :



(27% yield.)

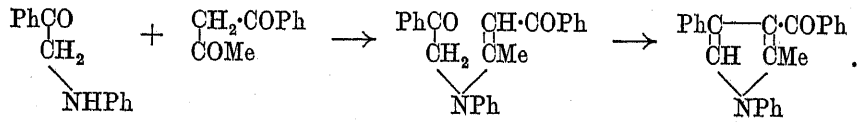
[1] *Ber.*, 1902, **35**, 2998–3008.
[2] *Ibid.*, 1910, **43**, 493.
[3] Piloty and Blömer, *ibid.*, 1912, **45**, 3750.
[4] *Ibid.*, 1983.

Even with this precaution, however, secondary products may be formed. From aminoacetophenone and acetylacetone Almström obtained, not only 2-methyl-3-acetyl-4-phenylpyrrole (I), but also a small amount of 2 : 4-dimethyl-5-benzoylpyrrole : [1]

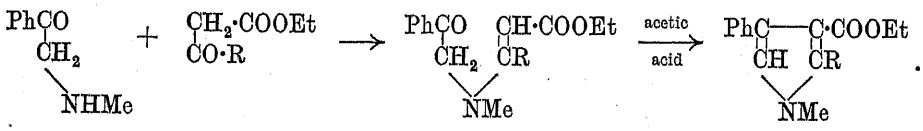


i.e. either the benzoyl- or the acetyl-carbonyl may take part in the final dehydration.

The reaction has been extended by Almström [2] to secondary α-aminoketones :

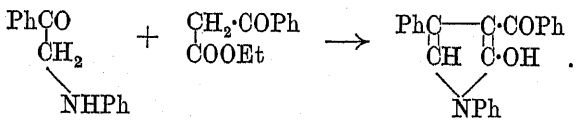


The intermediate tertiary aminoketone may in certain cases be isolated by performing the condensation without a solvent; the pyrrole is obtained when this intermediate is heated with acetic acid :



(R = Me or Ph.)

The condensation of phenacylaniline with benzoylacetic ester takes an abnormal course : [3]

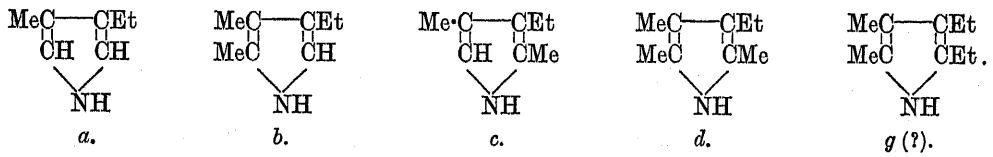


Pyrrolones are similarly formed from *p*-tolacylaniline and benzoylacetic ester and from phenacyl-β-naphthylamine and acetoacetic ester.

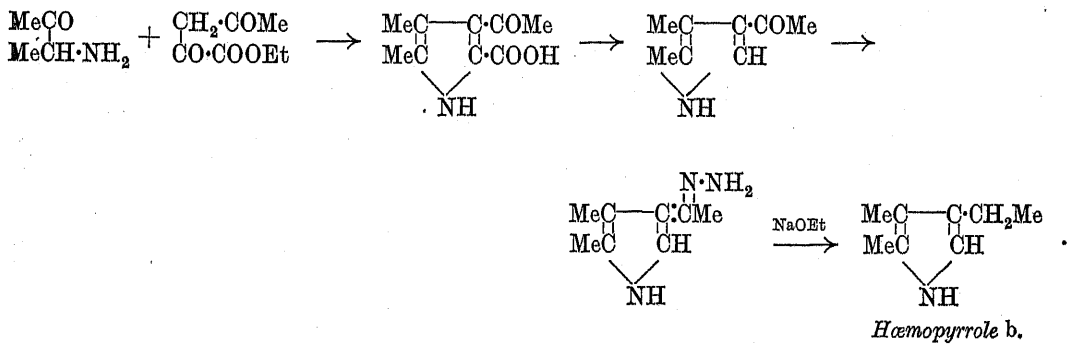
An interesting application of the Knorr-Piloty method is the synthesis of the various alkylated pyrroles obtained from hæmin (the first degradation product of hæmoglobin) by reduction with hydriodic acid and phosphonium iodide in acetic acid. These hæmopyrroles may also be prepared from chlorophyll.[4]

[1] *Ann.*, 1915, **409**, 302.
[2] *Ibid.*, pp. 291–305; 1916, **411**, 350–382.
[3] Almström, *ibid.*, p. 363.
[4] See Piloty, Stock and Dormann, *ibid.*, 1914, **406**, 342–374; and for a review of the subject to August 1912 see Hahn, *Zeitschr. Biol.*, 1914, **64**, 141.

Of the seven hæmopyrroles four have been synthesised and a fifth is probably identical with H. Fischer and Bartholomäus' 2 : 3-dimethyl-4 : 5-diethylpyrrole : [1]

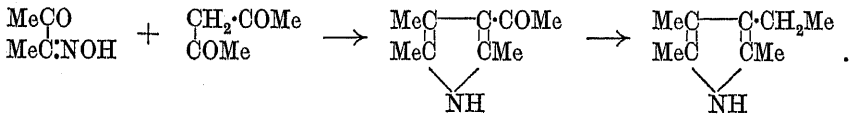


Hæmopyrrole *a* was synthesised from methylethylmaleinimide by distillation with zinc dust and lime.[2] For hæmopyrrole *b* Piloty and Blömer [3] condensed aminobutanone with acetylpyruvic ester (pyruvic ester fails to give a pyrrole), the acetyl group being subsequently reduced by Wolff's method :



Hæmopyrrole b.

By a similar synthesis from *iso*nitrosoacetone and acetylacetone, Knorr and Lange [4] obtained hæmopyrrole *c* (H. Fischer's cryptopyrrole). Hæmopyrrole *d* (Willstätter's phyllopyrrole) may be prepared from cryptopyrrole by methylation with NaOMe at 210–220°,[5] or it may be synthesised from *iso*nitrosoethyl methyl ketone and acetylacetone, the acetyl group being reduced to C_2H_5 with sodium amalgam : [6]

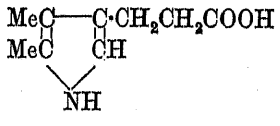


Hæmopyrrole d.

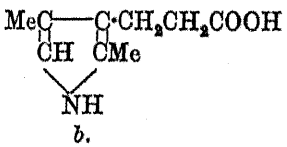
Hæmopyrrole *e* is probably 1 : 3-dimethyl-2-ethylpyrrole; the structures of *e*, *f* and *g* are not, however, determined with certainty.

[1] *Ber.*, 1912, **45**, 1983. [2] Grabovski and Marchlewski, *ibid.*, 1914, **47**, 2159.
[3] *Ibid.*, 1912, **45**, 3750. [4] *Ibid.*, 1902, **35**, 3001; Willstätter and Asahina, *ibid.*, 1911, **44**, 3707.
[5] H. Fischer and Bartholomäus, *ibid.*, 1912, **45**, 469. [6] Colacicchi, *R. A. L.*, 1912, [iv], **21**, i, 489.

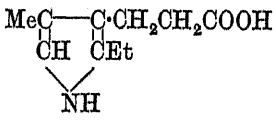
The phonopyrrolecarboxylic acids *a*, *b*, *c* and *d* occur with the hæmopyrroles in the reduction product of hæmin and have the following structures :



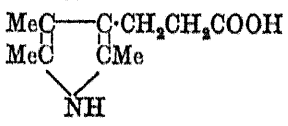
a.



b.



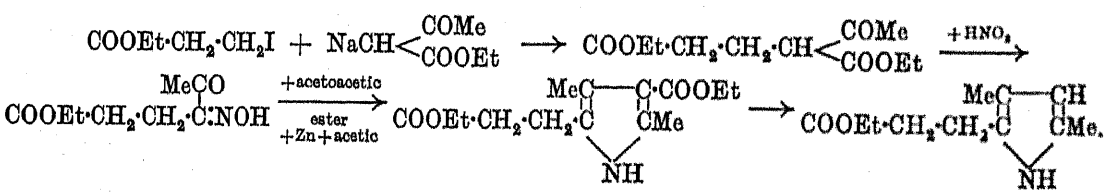
c.



d.

Their relationship to the hæmopyrroles is obvious.

The synthesis of these acids presents difficulties which have not yet been overcome, though a dimethylpyrrole-2-propionic acid has been prepared by H. Fischer and Bartholomäus : [1]



Pyrroles have been obtained from the following *iso*nitroso- or amino-ketones :

iso*Nitrosoketone.*	*Condensed with*	*Yield.*	*References.*
MeCO CH:NOH	Acetylacetone.	33%	6, 8
	Acetoacetic ester.	50%	6
MeCO MeC:NOH	Acetylacetone.	—	9, 10
	Dipropionylmethane.	27%	12
	Acetoacetic ester.	—	7
MeCO Et·C:NOH	Dipropionylmethane.	60%	17
	Acetoacetic ester.	—	7, 10
EtCO MeC:NOH	Acetylacetone.	55–60%	16
	Acetoacetic ester.	—	16
MeCO Pr·C:NOH	Acetoacetic ester.	—	7
MeCO MeCO·C:NOH	Acetoacetic ester.	—	3, 4
PhCO CH:NOH	Acetylacetone.	40%	6
	Benzoylacetone.	45%	6
	Acetoacetic ester.	56%	6
	Acetonedicarboxylic ester.	3%	6

[1] *Ber.*, 1912, **45**, 1925.

iso-*Nitrosoketone.*	*Condensed with*	*Yield.*	*References.*
PhCO PhC:NOH	Acetylacetone.	58%	6
	Acetoacetic ester.	25%	6
MeCO COOEt·C:NOH	Acetoacetic ester.	30%	1, 2
	Acetoacetic anilide.	—	2
	Acetylacetone.	—	3, 4
MeCO PhNH·CO·C:NOH	Acetoacetic ester.	—	2
	Acetoacetic anilide.	—	2
$COOEt·CH_2·CO$ COOEt·C:NOH	Acetonedicarboxylic ester.	—	5
MeCO $COOEt·CH_2·C$:NOH	Acetoacetic ester.	39%	11
MeCO $COOEt·CH_2CH_2·C$:NOH	Acetoacetic ester.	48%	11

α-*Aminoketone.*	*Condensed with*	*Yield.*	*References.*
MeCO $CH_2·NH_2$	Acetone.	30%	15
	Methyl ethyl ketone.	28%	15
	Diethyl ketone.	—	15
	Acetophenone.	15%	15
	Acetoacetic ester.	—	15
	Oxalacetic ester.	—	15
	Acetylpyruvic ester.	—	14
MeCO $MeCH·NH_2$	Acetone.	50%	15
	Methyl ethyl ketone.	small	15
	Oxalacetic ester.	—	13, 15
	Acetylpyruvic ester.	—	14
EtCO $MeCH·NH_2$	Oxalacetic ester.	—	13
PhCO $CH_2·NH_2$	Acetone.	—	6
	Acetylacetone.	100%	6, 18
	Benzoylacetone.	38%	6
	Phenylacetone.	trace	6
	Acetoacetic ester.	100%	6
	Acetonedicarboxylic ester.	9%	6
	Acetylpyruvic ester.	trace	6
HCO $MeCH·NHMe$	Acetonedicarboxylic ester.	—	20
PhCO $CH_2·NHMe$	Acetylacetone.	—	18
	Acetoacetic ester.	—	19
PhCO $CH_2·NHPh$	Acetylacetone.	70%	18
	Benzoylacetone.	40%	18
	Acetoacetic ester.	45%	19
$p·C_7H_7·CO$ $CH_2·NHPh$	Acetylacetone.	25%	18
	Benzoylacetone.	14%	18
	Acetoacetic ester.	—	29

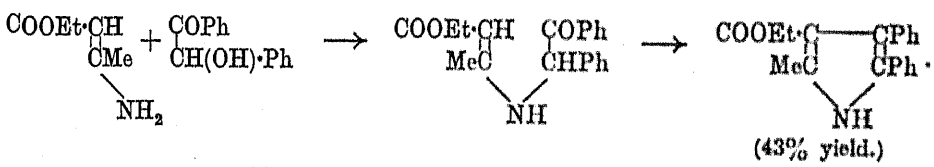
References.

[1] Knorr, *Ber.*, 1884, **17**, 1638. [2] *Idem*, *Ann.*, 1886, **236**, 317. [3] Zanetti, *R. A. L.*, 1893, [v], **2**, i, 324. [4] Zanetti and Levi, *Gazz.*, 1894, **24**, i, 546. [5] Feist, *Ber.*, 1902, **35**, 1556. [6] Knorr and Lange, *ibid.*, pp. 2998–3008. [7] Knorr and Hess,* *ibid.*, 1911, **44**, 2761–2767. [8] Willstätter and Asahina, *ibid.*, p. 3707. [9] H. Fischer and Bartholomäus, *Ztschr. physiol. Chem.*, 1912, **77**, 185–201. [10] Colacicchi, *R. A. L.*, 1912, [iv], **21**, i, 489. [11] H. Fischer and Bartholomäus, *Ber.*, 1912, **45**, 1925. [12] *Idem*, *ibid.*, p. 1983. [13] Piloty and Wilke, *ibid.*, pp. 2587–2591. [14] Piloty and Blömer, *ibid.*, p. 3750. [15] Piloty and Hirsch, *Ann.*, 1913, **395**, 65–74. [16] Vecchi, *Gazz.*, 1914, **44**, i, 473–479. [17] H. Fischer and Eismayer, *Ber.*, 1914, **47**, 1826. [18] Almström, *Ann.*, 1915, **409**, 291–305. [19] *Idem*, *ibid.*, 1916, **411**, 361, 364, 367. [20] Willstätter and Pfannenstiel, *ibid.*, 1921, **422**, 10.

* Certain products are wrongly named in this paper:
p. 2763, should be 2 : 4-dimethyl-5-ethyl-pyrrole-3-carboxylic ester.
p. 2764, should be 2 : 4-dimethyl-5-propyl-pyrrole-3-carboxylic ester.

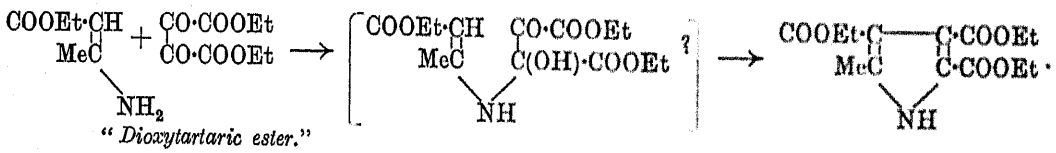
17. From β-aminocrotonic ester: 

This method, due to Feist and Stenger,[1] was suggested by Knorr's synthesis from *iso*nitroso-ketones, but is of very limited application. β-Aminocrotonic ester was condensed with benzoin at 110° and the product was heated with a little $KHSO_4$ at 140–150° to close the ring:



(43% yield.)

Feist and Stenger next tried α-diketones in place of benzoin. Diketosuccinic ester was heated with β-aminocrotonic ester and a little $KHSO_4$ to 130–140° and the product reduced with zinc and acetic acid:

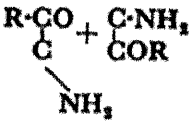


"*Dioxytartaric ester.*"

The yield was only 17%. Diacetyl, benzil and phenanthraquinone all failed to give satisfactory results.

[1] *Ber.*, 1902, **35**, 1559.

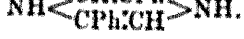
18. From α-aminoketones :



By a reaction related to the Knorr synthesis the salts of α-aminoketones are converted into 3-aminopyrroles by the action of concentrated alkali : [1]



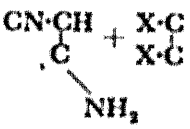
The main product is, however, the dihydropyrazine :



In the case of α-amino*iso*propyl methyl ketone, a pyrrolenine is probably formed : [2]



19. From "dinitriles" and α-hydroxyacids :

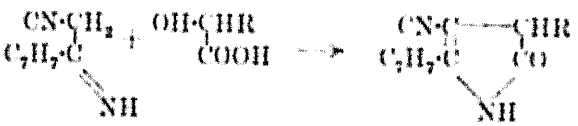


Benzoacetodinitrile (β-amino-β-phenylacrylic nitrile) condenses with mandelic or lactic acid to form a β-pyrrolone : [3]



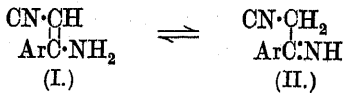
(R = Me or Ph.)

The reaction takes a different course in the case of *p*-toluacetodinitrile, the product being here an α-pyrrolone :



[1] Gabriel, *Ber.*, 1908, **41**, 1138. [2] *Idem*, *ibid.*, 1911, **44**, 65. [3] E. v. Meyer, *J. pr. Chem.*, 1914, **90**, 1.

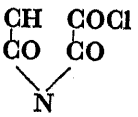
This difference is possibly due to a difference in the proportions of the two forms of the dinitrile present:



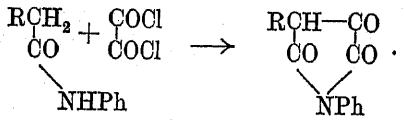
(I.) (II.)

If (II) predominates, the reactive ·CH_2· group will have the greater chance of reacting with the alcoholic ·OH group and an α-pyrrolone will result.

20. From acylated anilines and oxalyl chloride:

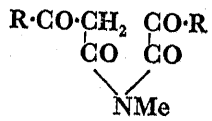


The action of oxalyl chloride upon propionanilide and upon phenylacetanilide has been studied by Figee.[1] The products are triketopyrrolidines:

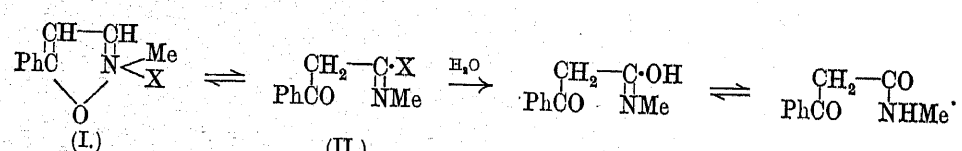


(R = Me or Ph.)

21. From 5-methyl- and 5-phenyl-*iso*oxazoles:



The methiodide or methosulphate of 5-phenyl*iso*oxazole (I) reacts also in the form of the open chain compound (II).[2] Under hydrolytic conditions this readily passes into the β-ketoamide (III):

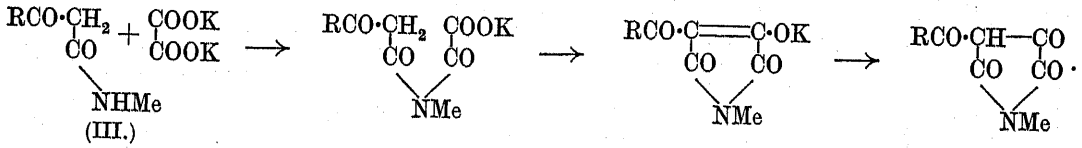


(I.) (II.) (III.)

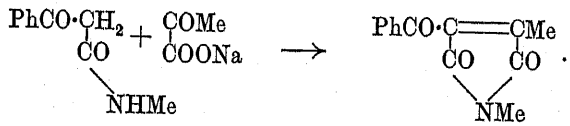
The application of this compound to the synthesis of 2-phenyl-4 : 5-diketopyrroline by Mumm and Münchmeyer has already been described (p. 37). Mumm and Bergell [3] have condensed the methosulphate with potassium oxalate in aqueous solution at room temperature, the

[1] *Rec. trav. chim.*, 1915, **34**, 289–325. [2] Claisen, *Ber.*, 1909, **42**, 67. [3] *Ibid.*, 1912, **45**, 3152.

product being 1-methyl-3-benzoyltriketopyrrolidine. 5-Methyl*iso*oxazole methosulphate behaves similarly :

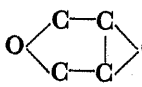


Sodium pyruvate reacts with phenyl*iso*oxazole methosulphate to form the corresponding benzoylmethylmaleic methylimide : [1]

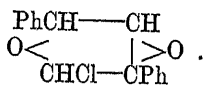


From sodium cinnamate only the imide (IV) was obtained. This showed no tendency to isomerise to the succinimide (V) :

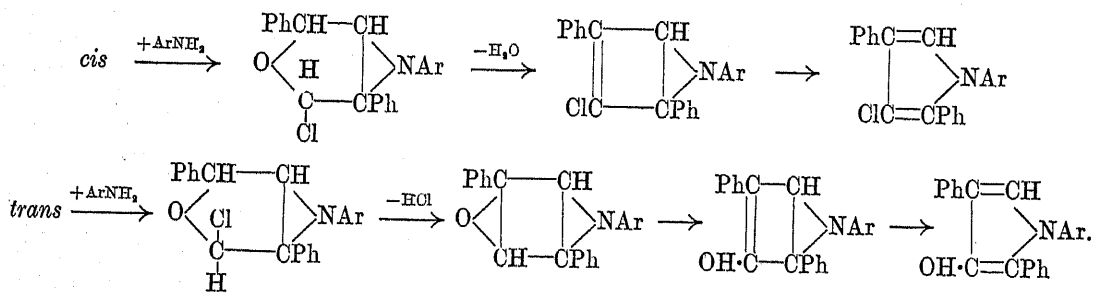


22. From chlorodiphenacyls:  + NH_2Ar

ω-Chloroacetophenone is converted by NaOEt into a mixture of α- and β-chlorodiphenacyls,[2] which have been shown by Widman [3] to be *cis*- and *trans*-forms respectively of :

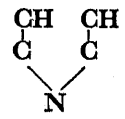


By the action of aniline or *p*-toluidine they are converted into pyrrole derivatives by a curious series of reactions interpreted by Widman as follows :

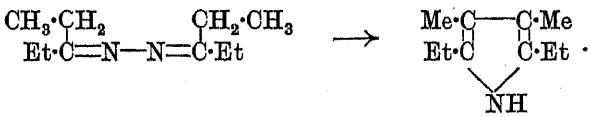


(Ar = phenyl or *p*-tolyl.)

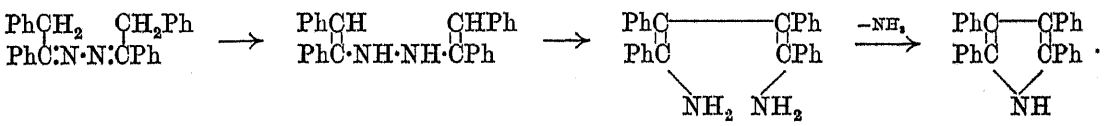
[1] Knust and Mumm, *Ber.*, 1917, **51**, 567.
[2] Städel and Rügheimer, *ibid.*, 1876, **9**, 1758.
[3] *Ann.*, 1913, **400**, 106.

23. From the azines of enolisable ketones: 

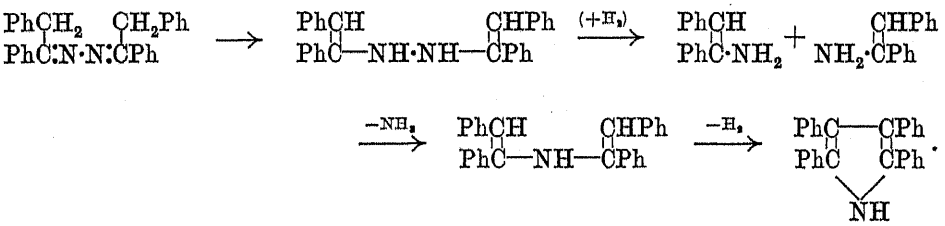
This method is analogous to Fischer's indole synthesis. The first example was described by Piloty,[1] who obtained 2 : 5-diethyl-3 : 4-dimethylpyrrole in 28% yield by heating the azine of diethyl ketone with zinc chloride :



Robinson and Robinson,[2] in support of their azine theory of the mechanism of the Fischer indole synthesis (see p. 94), showed that the azines of readily enolisable ketones of the type $R{\cdot}CH_2{\cdot}CO{\cdot}R$ gave pyrroles when heated with dry HCl at 180°. Tetraphenylpyrrole was obtained quantitatively from desoxybenzoin, but from aliphatic ketones the yield was smaller owing to the formation of pyrazolines. Robinson and Robinson suggested the following mechanism for the reaction :

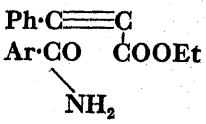


It seems more probable, however, for the reasons stated on p. 94, that the reaction takes the following course :

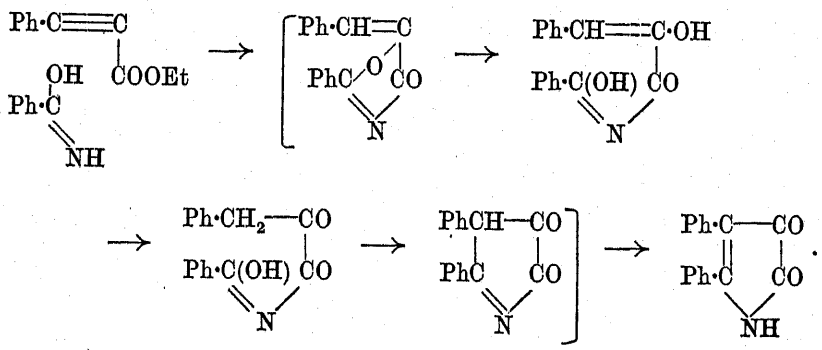


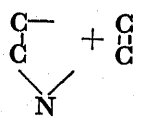
[1] *Ber.*, 1910, **43**, 497.

[2] *J. C. S.*, 1918, **113**, 639.

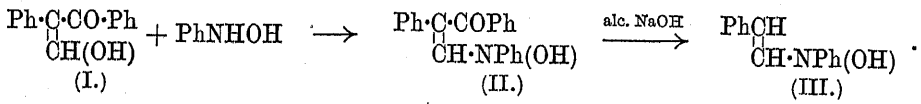
24. From phenylpropiolic ester and aromatic amides : 

The sodio-derivatives of aliphatic amides react with phenylpropiolic ester to form diacylimides. With aromatic amides a different reaction occurs and the products are diketopyrrolines.[1] A possible mechanism for this curious reaction is the following :



25. From hydroxymethylene-desoxybenzoin and phenylhydroxylamine : 

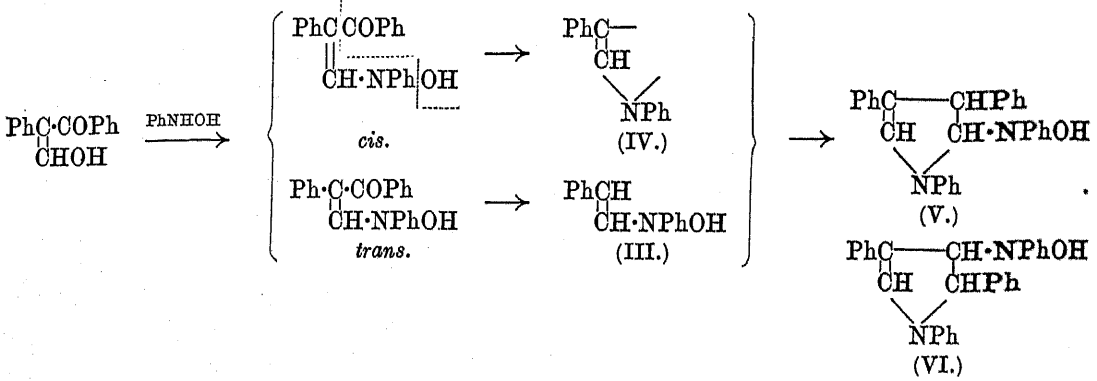
This very suggestive reaction has recently been described by Rupe and Wittwer.[2] Hydroxymethylene-desoxybenzoin (I) reacts with phenylhydroxylamine to form phenylhydroxylaminobenzoylstyrene (II). In alcohol the *cis*-isomeride is produced; in acetic acid, the acetyl derivative of the *trans*-isomeride, from which the acetyl group may be eliminated by treatment with dilute H_2SO_4 and alcohol. Alcoholic aqueous NaOH removes the benzoyl group and gives phenylhydroxylaminostyrene (III) :



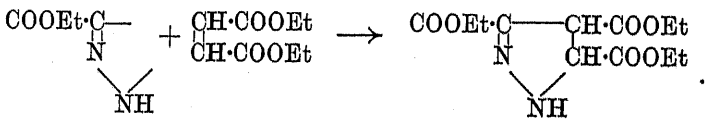
When the reaction takes place in the *absence* of a solvent, the product is 1 : 3 : 4-triphenyl-2-phenylhydroxylaminopyrroline (V). Under such conditions both the *cis*- and the *trans*-isomerides would be formed equally easily. The *cis*-compound by elimination of PhCO·OH gives

[1] Ruhemann, *J. C. S.*, 1909, **95**, 954, 984, 1603; *cf.* Ruhemann and Merriman, *ibid.*, 1905, **87**, 1383.
[2] *Helv. Chim. Acta*, 1922, **5**, 205–216.

momentarily a substance (IV) with two free valencies, and this at once adds itself at the double bond of the *trans*-compound, which meanwhile has been hydrolysed to the styrene (III) :

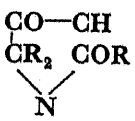


It will be seen that the final reaction is analogous to the Buchner synthesis of pyrazolines from diazoacetic ester :

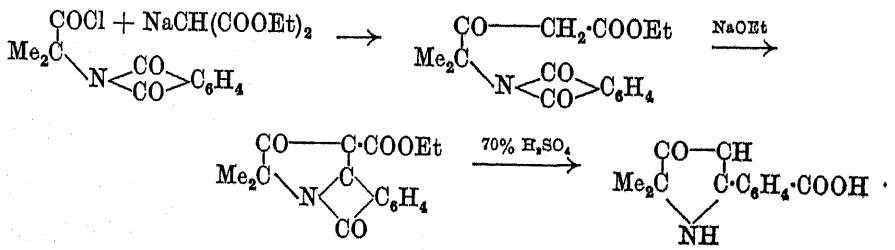


The alternative structure (VI) is regarded as less probable than (V). The same compound is obtained by treating the *cis*-isomeride with alkali, while $SOCl_2$ converts both the *cis*-isomeride and the compound (V) into the corresponding pyrroline, in which ·OH is replaced by Cl.

26. From acylated α-aminoketones :

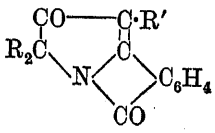


In the preparation of α-amino*iso*propyl methyl ketone by the phthalimide method, Gabriel [1] found that the condensation of phthaliimino*iso*butyryl chloride with sodiomalonic ester gave a pyrrolone as by-product. This became the main product when excess of sodiomalonic ester (or of NaOEt) was used :



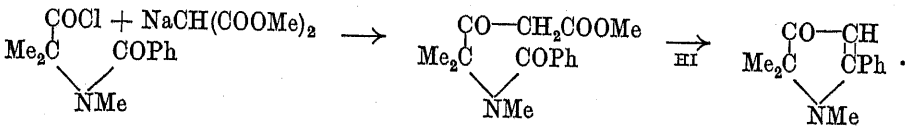
[1] *Ber.*, 1911, **44**, 62, 70.

It was later discovered [1] that this reaction occurs only with *gem*-dialkyl derivatives,* though the malonic ester group may be replaced by other groupings such as ·CH(CN)COOEt, ·CH_2CN, ·CH_2CONH_3 and even ·CH_3, giving the compounds:

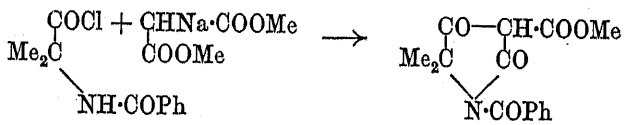


(R = Me or Et
R′ = ·CN, ·$CONH_2$ or H.)

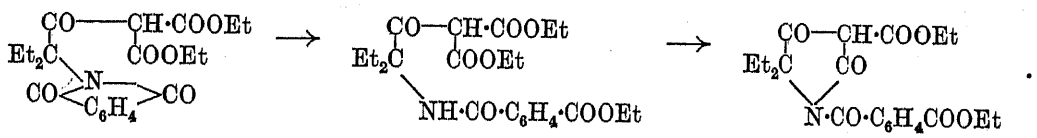
Further, it was found that the *benzoyl* derivative of methylamino*iso*butyrylmalonic ester could be condensed to trimethylphenylpyrrolone. Here the ring-closure is brought about, not by NaOEt, but by hydriodic acid:



In the absence of the *N*-methyl group a different condensation occurs, resulting in the formation of a 2 : 4-diketopyrrolidine: [2]



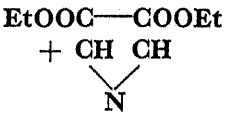
A diketopyrrolidine was also obtained by Pfähler [3] from a phthalimino-derivative:



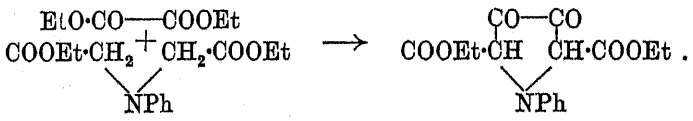
The pyrrolone formation is here a subsidiary reaction. The corresponding methyl-ethyl derivative behaves similarly.

[1] Gabriel, *Ber.*, 1913, **46**, 1321–1358; Pfähler, *ibid.*, pp. 1709–1714.
[2] Gabriel, *ibid.*, p. 1352. [3] *Loc. cit.*
* It is interesting to compare this with the easy formation of *cyclo*propane and *cyclo*butane rings from *gem*-dialkyl compounds (Ingold and Thorpe, *J. C. S.*, 1920, **117**, 1579, etc.).

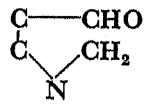
27. From iminodiacetic ester and oxalic ester:



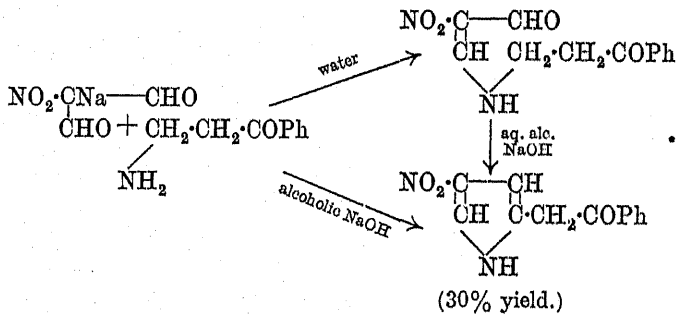
de Mouilpied [1] condensed phenyliminodiacetic ester with oxalic ester by means of NaOEt and obtained a compound, $C_{16}H_{17}O_6N$, which Johnson and Bengis [2] showed to be a 3 : 4-diketo-pyrrolidine derivative:



28. From β-alkylamino-aldehydes:

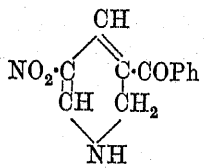


A remarkable closure of the pyrrole ring in the α : β-position is recorded by Hale and Britten,[3] who condensed sodio-nitromalonic aldehyde with β-aminopropiophenone:

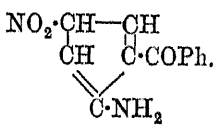


(30% yield.)

The absence of any pyridine derivative (I) in the product is unexpected. The ·CH_2· adjacent to the benzoyl group does react, but only to form the *cyclo*pentadiene by-product (II):



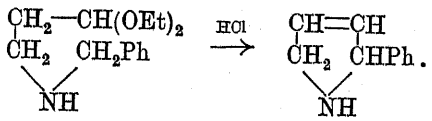
(I.)



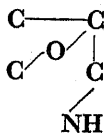
(II.)

[1] *J. C. S.*, 1905, **87**, 435. [2] *J. A. C. S.*, 1911, **33**, 745. [3] *Ibid.*, 1919, **41**, 1020.

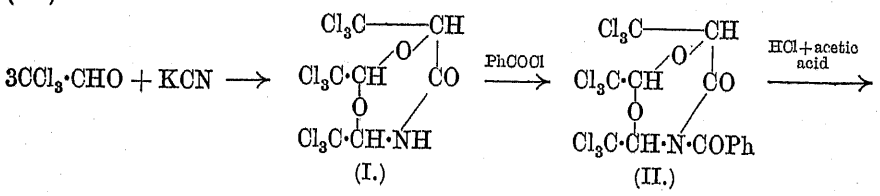
A very similar type of ring-closure occurs when benzyl-β-aminopropionacetal is treated with conc. HCl : [1]

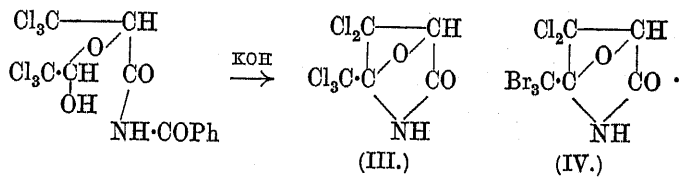


29. From chloral hydrate and potassium cyanide:



The action of KCN upon chloral hydrate, first studied by Wallach [2] and Cech,[3] has been elucidated by Crowther, McCombie and Reade,[4] who obtained in 30–40% yield an anhydro-compound, $C_7H_4O_3NCl_9$ (I). This was benzoylated in the presence of pyridine, and successive treatment of the product (II) with acid and alcoholic KOH gave the pyrrolidone derivative (III) :

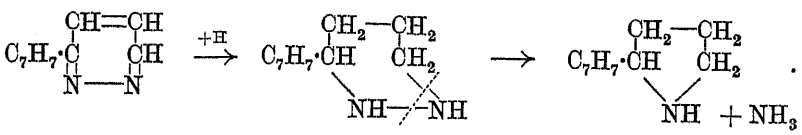




A mixture of bromal, chloral cyanhydrin and KOH yielded a similar series of products, leading to the pyrrolidone (IV).

30. From pyridazines

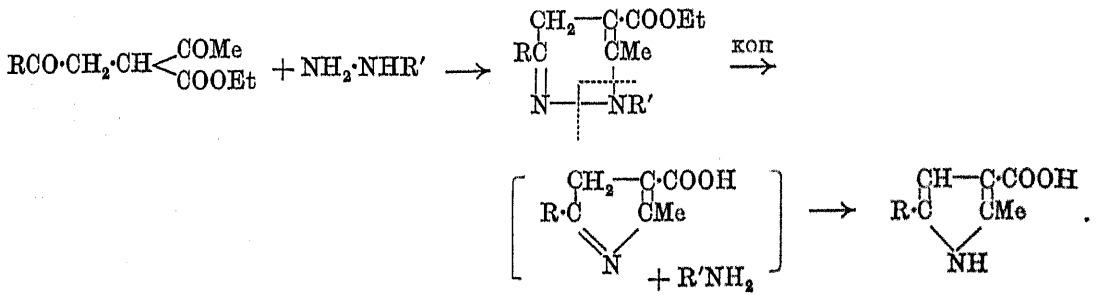
By reduction of *p*-tolylpyridazine with sodium amalgam, Katzenellenbogen [5] obtained the hexahydro-derivative and, at the same time, 2-tolylpyrrolidine by elimination of a nitrogen atom as ammonia :



[1] Wohl, *Ber.*, 1901, **34**, 1922. [2] *Ann.*, 1874, **173**, 297. [3] *Ber.*, 1876, **9**, 1020.
[4] *J. C. S.*, 1914, **105**, 933–946. [5] *Ber.*, 1901, **34**, 3837.

The reaction is quite analogous to the formation of *iso*indoles by the reduction of phthalazines (see p. 162).

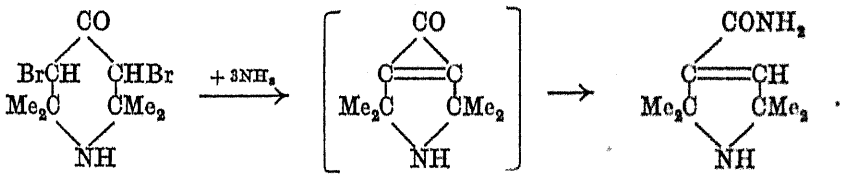
Borsche and Spannagel [1] prepared dihydropyridazines by the action of phenylhydrazine or semicarbazide upon phenacyl- and acetonyl-acetoacetic esters. The products were converted into pyrroles when heated with alkali :



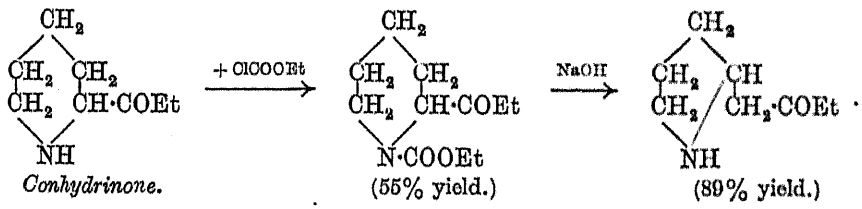
(R = Me or Ph; R′ = Ph or ·$CONH_2$.)

31. From pyridines

The first direct conversion of a pyridine derivative into a pyrrole was Pauly's preparation of 2 : 2 : 5 : 5-tetramethylpyrroline-3-carboxylic amides by the action of ammonia, methylamine or dimethylamine upon the dibromo-derivative of triacetonamine : [2]



The *N*-carboxylic ester of conhydrinone yields α-pyrrolidylmethyl ethyl ketone when heated for five minutes with aqueous-alcoholic NaOH : [3]

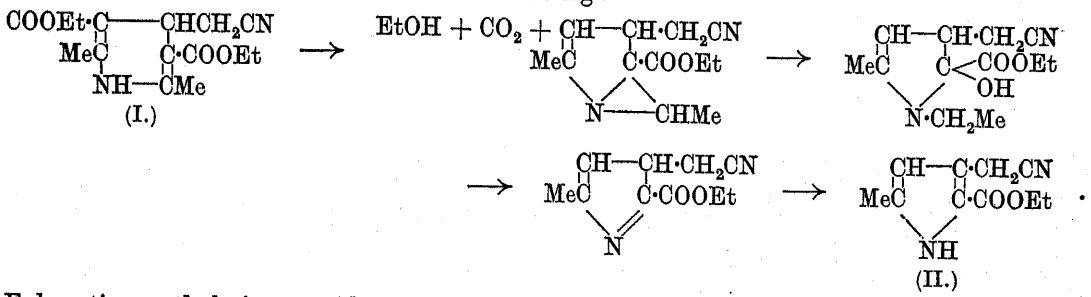


Conhydrinone. (55% yield.) (89% yield.)

Benary [4] obtained 2-methyl-4-cyanomethylpyrrole-5-carboxylic ester (II) in 70% yield by

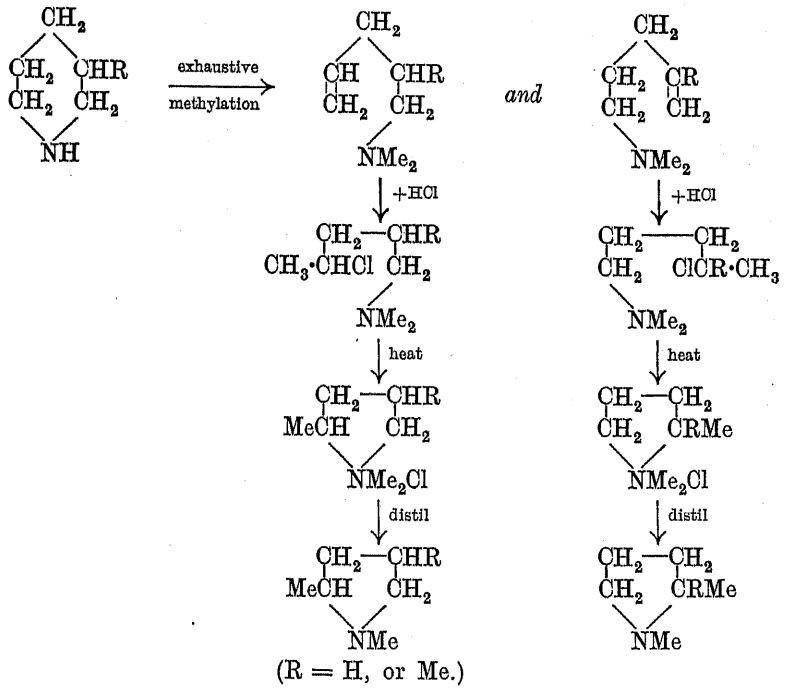
[1] *Ann.*, 1904, **331**, 310, 317.
[2] D.R.-P. 109345; *Ber.*, 1898, **31**, 2000; 1900, **33**, 919, 2224; *Ann.*, 1902, **322**, 77–130.
[3] Hess, *Ber.*, 1919, **52**, 1630.
[4] *Ibid.*, 1920, **53**, 2218.

the action of alcoholic KOH upon 4-cyanomethyl-dihydrocollidinedicarboxylic ester (I). A possible mechanism for this reaction is the following :



(I.) (II.)

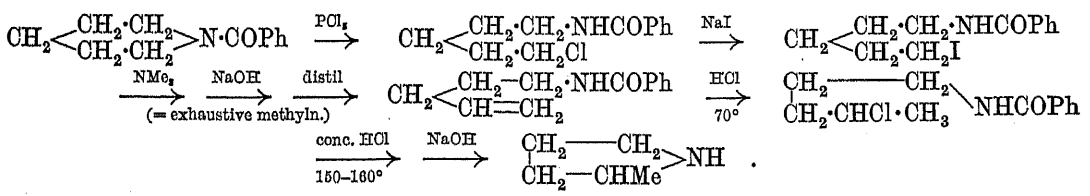
Exhaustive methylation provides a method of passing from the piperidine series to pyrrolidines. The unsaturated amine undergoes cyclisation when heated with conc. HCl : [1]



(R = H, or Me.)

The method fails with α-alkylated piperidines.

v. Braun [2] converted piperidine into 2-methylpyrrolidine by a long series of reactions commencing with the opening of the ring by benzoylation followed by treatment with PCl_5 :

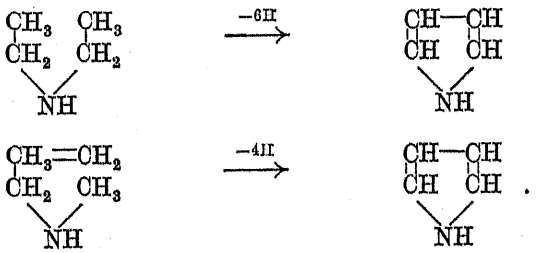


[1] Merling, *Ann.*, 1891, **264**, 315; Jacobi and Merling, *ibid.*, 1894, **278**, 8. [2] *Ber.*, 1910, **43**, 2864.

Ruzicka's conversion of β-cinchoninoyl-*N*-methyl-α-piperidone into α-cinchoninoyl-*N*-methylpyrrolidine by hydrolysis, bromination and removal of HBr has already been mentioned (see p. 68).

32. Pyrogenous methods

Diethylamine vapour gives appreciable quantities of pyrrole when passed through a hot tube, as does allylmethylamine passed over heated litharge :

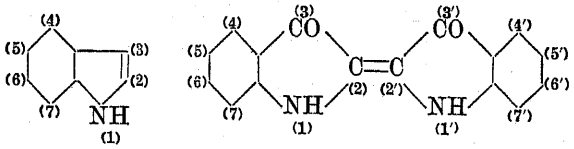


Dewar [1] obtained traces of pyrrole when a mixture of ammonia and acetylene (containing some ethylene) was led through a hot tube. The effect of catalysts has been studied by Tschitschibabin,[2] who passed acetylene and ammonia over oxides of aluminium, iron and chromium at 300°. Ferric oxide gives more pyrrole than does alumina.

[1] *Proc. Roy. Soc.*, 1877, **26**, 65. [2] *J. Russ.*, 1915, **47**, 703; *Zentr.*, 1916, **i**, 920.

CHAPTER IV

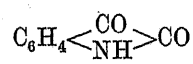
INDOLES AND INDIGOS,



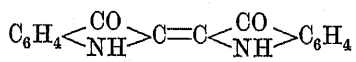
Introductory :

In this chapter no distinction is made between syntheses leading to simple indole derivatives and those leading directly to indigos. It will be useful therefore to indicate here the methods by which compounds of the one class may be converted into compounds of the other.

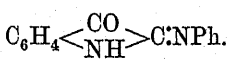
(*a*) *Indigos from indoles.*—The conversion of isatin into indigo by reduction with ammonium sulphide was first described by v. Baeyer : [1]



Isatin.



Indigo.



Isatin-α-anilide.

Better results are obtained with isatin-α-anilide.[2]

Indole may be oxidised to indigo by means of ozone.[3] By this method, using an acetone solution of indole, Weissgerber [4] obtained a 33% yield of indigo. A rather higher yield results when the oxidation is performed with iodine and sodium bicarbonate.[5] Permonosulphuric acid has also been employed,[6] but other oxidants, such as H_2O_2, CrO_3, HNO_3, $KMnO_4$ and $FeCl_3$, are useless.

The bisulphite compound of indole gives an appreciable yield of indigo by air oxidation,[7] and indole-3-carboxylic acid, prepared by Kolbe's reaction from sodio-indole and CO_2, is oxidised smoothly to indigo by ozone.[8]

(*b*) *Simple indole derivatives from indigos.*—The oxidation of indigo to isatin by nitric acid has long been known—Laurent and Erhardt discovered isatin by this method in 1841—but the yield is only 25%.[9] Oxidation with chromic acid alone is equally unsatisfactory,[10] but in the presence of oxalic acid 62% of isatin is said to be obtained.[11] The best oxidant appears to be a mixture of nitric acid and chromic acid, for which a yield of 85% is claimed.[12] The chromic acid method has been applied to halogenated indigos by Grandmougin and Seyder.[13]

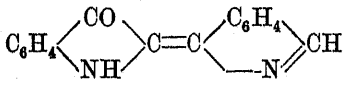
The indoxyl melt may also be oxidised to isatin.[14]

Bromo- and dibromo-isatins are obtained in good yield by treating indigo with sodium bromide and conc. H_2SO_4.[15]

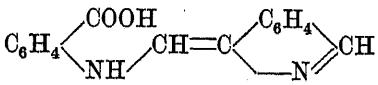
The conversion of indigo into indole itself is more difficult. A certain amount of indole is formed when phenylglycine or its *o*-carboxylic acid is "over-melted." [16] At 120°, there is

[1] *Ber.*, 1878, **11**, 1297; 1879, **12**, 457; 1883, **16**, 2203. [2] D.R.-PP. 119280, 119831, 175423.
[3] Nencki, *Ber.*, 1875, **8**, 727; Engler and Janecke, *ibid.*, 1876, **9**, 1414; D.R.-P. 230542.
[4] *Ber.*, 1913, **46**, 658. [5] Pauly and Gundermann, *ibid.*, 1908, **41**, 4007.
[6] Nencki, *ibid.*, 1874, **7**, 1593; D.R.-P. 132405. [7] D.R.-P. 130629. [8] D.R.-P. 230542.
[9] Ferrer, *Ber.*, 1884, **17**, 976. [10] Sommaruga, *Ann.*, 1878, **190**, 369.
[11] v. Georgevics and Springer, *Monatsh.*, 1900, **21**, 413. [12] D.R.-P. 229815.
[13] *Ber.*, 1914, **47**, 2365–2399. [14] D.R.-P. 107719. [15] Fr. Pat. 490281/1917.
[16] D.R.-P. 260327; E.P. 14943.

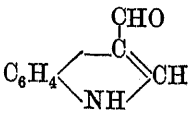
formed the dyestuff (I), which is hydrolysed by alkali at 240°, first into (II) and then into anthranilic acid and 3-aldehydo-indole (III),



(I.)



(II.)



(III.)

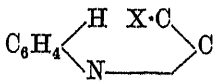
from which indole results by air oxidation and loss of CO_2.

The glycine melts yield indole when iron or sodium is added to the alkali at 300°.[1] Vorländer and Apelt [2] reduced the indoxylic acid melt with sodium amalgam at 60–70° and obtained a yield of indole corresponding to 55% of the possible indigo.

The methods available for the synthesis of indoles and indigos may be grouped as follows :

I. *Ring-closure between the β-Carbon Atom and the Benzene Nucleus*

Syntheses in this group (sects. 1–10) usually involve the elimination of HX from a compound of the type



—where X is halogen, ·OH or ·NHAr. The Fischer synthesis (sect. 1) is, on the other hand, a dehydrogenation (X = H); * it has been widely employed for the preparation of *indoles* and has been extended by Brunner to the synthesis of *oxindoles*.

In Knoevenagel's method (sect. 2) X = ·NHAr and the products are 2 : 2 : 3 : 3-*tetramethyl-indolines*.

The conversion of oxanilides into *isatins* (sect. 3) gave poor results until the discovery of Stollé's oxalyl chloride method, which is especially useful for the preparation of *N*-substituted isatins. Ordinary *isatins*, with no substituent on the nitrogen atom, are more easily prepared by either of the two Sandmeyer syntheses (sects. 4 and 5).

α-Phenylindoles are obtained from phenacylarylamines (sect. 6), and similar reactions lead to *indole* and to other α-substituted derivatives.

Knorr's pyrrole synthesis has been extended to the preparation of *indoles* with a reduced benzene nucleus (sect. 7).

The only method of this group, besides Bauer's and Stollé's (sect. 3), in which X = halogen is the preparation of *oxindoles* from chloroacetylated arylamines (sect. 8). Flimm's *indigo* synthesis, which proceeds *via* phenylglycine, is dealt with in the same section.

Methods depending on the alkaline fusion of arylglycines (sect. 9) are of first importance for the technical preparation of *indoxyls* and *indigos*. *Indoxylic esters* are obtainable from aryl-aminomalonic esters (sect. 9) by a similar condensation under the influence of heat alone.

Hinsberg's synthesis (sect. 10) from glyoxal and arylamines leads to *oxindoles*, *indoles* and *indolines*, but is of somewhat limited application.

[1] D.R.-P. 152683. [2] *Ber.*, 1904, **37**, 1134.

* If Robinson and Robinson's theory of the mechanism is correct (see p. 94), Fischer's synthesis should be classed with those in group III.

II. *Ring-closure between α- and β-Carbon Atoms*

In all but one of the six methods in this group ring-closure occurs by the elimination of water (or alcohol).

The cheap catalytic process for phthalic anhydride by air oxidation of naphthalene has made anthranilic acid once more a very important starting-material for the commercial synthesis of *indigos* by Heumann's second method (sect. 11) or the later formaldehyde–cyanide process. Other *indoxyl* and *indigo* syntheses from *N*-methylanthranilic acid derivatives (sect. 12) are of minor interest.

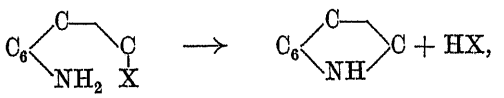
o-Cyanophenylglycine gives the imino-compound of *indoxylic acid* (sect. 13) by intramolecular addition at the ·C≡N group. *o*-Aldehydophenylglycine has been converted into *indole* by Gluud (sect. 14).

More useful than these is Madelung's synthesis of α-substituted *indoles* and *di-indyl* from acylated *o*-toluidines (sect. 15).

The dehydration of *iso*propyl-*o*-aminobenzyl alcohol to 2 : 2-*dimethylindoline* (sect. 16) is an isolated reaction which probably does not admit of extension.

III. *Ring-closure between Nitrogen and α-Carbon Atoms*

In this group are included the large number of indigo and indole syntheses from "ortho-nitro"-compounds by intramolecular oxidation and reduction (sects. 17, 18, 19, 20, 24, 26), and also ring-closures of the type



where X may be ·OH, ·OR, ·NHR or halogen.

Lipp's synthesis from *o*-aminostyryl halides leads to *indoles* (sect. 17A). *o*-Nitrostyrene derivatives also give *indoles* and N-*hydroxy-indolines* (sect. 17B) by internal oxidation. The isatogen reaction (sect. 18), by which *o*-nitrophenylacetylenes are converted into *isatins* or *indigos*, has led to interesting results in the hands of Pfeiffer and of Ruggli.

A useful and very general *indigo* synthesis is that from *o*-nitrobenzaldehydes and acetone (sect. 19). It may be modified in such a manner as to give *isatins*. N-*Hydroxyindole-α-carboxylic acids*, and hence *indoxylic acids*, *isatins*, *indoles* and *indigos*, are obtainable by Reissert's method (sect. 20) from *o*-nitrobenzylmalonic esters. The reduction of *o*-nitrobenzyl ketones (sect. 21) yields *indoles* with an α-substituent. *α-Aminoindole* is obtained by a "Thorpe reaction" from *o*-aminobenzyl cyanide (sect. 22).

Oxindoles are the lactams (or lactims) of *o*-aminoarylacetic acids (sect. 23), and *isatins* are similarly related to *o*-aminobenzoylformic acids (sect. 25). From *o*-nitromandelic acid may be prepared *dioxindoles*, *isatin* and *indigo* (sect. 24).

The first *indigo* synthesis—Emmerling and Engler's reduction of *o*-nitroacetophenone—and the related methods from *o*-nitrobenzoylacetic acid, are described in section 26.

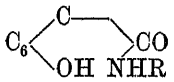
The elimination of hydrogen halide from *o*-aminophenacyl halides (sect. 27) yields *indoxyls*.

Martinet's synthesis of *dioxindolecarboxylic esters*, and hence of *isatins*, by the action of mesoxalic ester upon arylamines (sect. 28), is especially useful in the naphthalene series. In the

benzene series irregular results are obtained, the cause of which has not been explained. A synthesis involving a similar migration of large groups to an *ortho* position is the production of *isatins* from arylamines and dichloroacetic acid (sect. 29).

IV. *Ring-closure between Nitrogen and the Benzene Nucleus*

This group includes the preparation of 2-*phenylindoxyl* (or perhaps 2-*phenyl*-N-*hydroxyindole*) from benzoin oxime (sect. 30) and the formation of a *tetrahydro-oxindole* and a *tetrahydro-isatin* from amides of the type



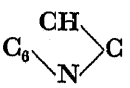
(sect. 31).

V. *Miscellaneous Syntheses*

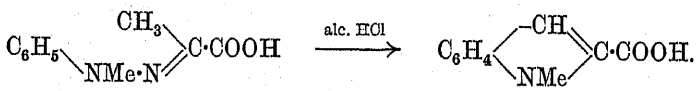
The formation of *indoles* by the attachment of a four-carbon chain to a pyrrole ring may be brought about in several ways (sect. 32), especially as pyrrole itself can supply a suitable four-carbon chain. The fission of the hydrogenated ring in tetrahydrocarbazoles may give *indoles* or *indoxyls*.

Quinolines may also serve as a source of *indoles*, *indolines*, *isatin* or *indigo* (sect. 33). *Indole* results when hydroxycinnoline is distilled with zinc dust (sect. 34).

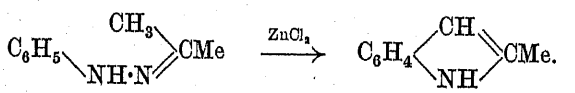
Finally certain pyrogenous reactions lead to *indoles* (sect. 35).

1. Fischer's synthesis from arylhydrazones: 

The first example of this important method was discovered by E. Fischer and Jourdan,[1] who boiled the methylphenylhydrazone of pyruvic acid with alcoholic HCl. The product, $C_{10}H_9O_2N$, proved on investigation [2] to be an indole derivative:



This reaction becomes very general if zinc chloride be substituted for alcoholic HCl as condensing agent.[3] The aldehyde or ketone is first treated with phenylhydrazine (or any arylhydrazine having a free *ortho* position) and the product is heated at 180–200° with about five times its weight of anhydrous $ZnCl_2$. From acetone phenylhydrazone Fischer obtained 2-methylindole ("methylketol") in 60% yield:



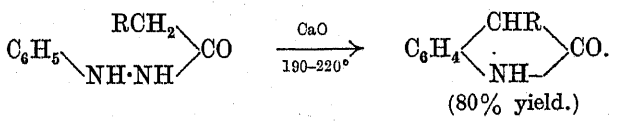
[1] *Ber.*, 1883, **16**, 2245.
[2] Fischer and Hess, *ibid.*, 1884, **17**, 559.
[3] Fischer, *ibid.*, 1886, **19**, 1567; *Ann.*, 1886–1889.

Much improved yields are claimed in D.R.-P. 238138. Here a solvent (naphtha or methylnaphthalene) is used and the temperature is not allowed to exceed 150°. Acetone in this way gives 75% of 2-methylindole; scatole is obtained in 80% yield from propionaldehyde (35% by Fischer's procedure), and pyruvic acid gives 60% of indolecarboxylic acid instead of only 5–6%.

Arbuzov and Tichvinski [1] showed that the large excess of $ZnCl_2$ employed by Fischer was unnecessary. The reaction is catalytic and proceeds in the presence of 1% of $ZnCl_2$, Cu_2Cl_2, Cu_2Br_2 or $PtCl_2$. These substances also catalyse the decomposition of phenylhydrazine into aniline, nitrogen and ammonia at 150° (aniline is observed as a by-product in the Fischer synthesis).

Other condensing reagents which bring about the reaction are conc. H_2SO_4,[2] alcoholic H_2SO_4,[3] alcoholic $ZnCl_2$,[4] and, in the case of acid hydrazides, lime [5] or NaOEt.[6]

Brunner [7] discovered that although $ZnCl_2$ had little action upon acid hydrazides of the type $PhNH{\cdot}NH{\cdot}CO{\cdot}CH_2R$, these could be converted into oxindoles by heating for an hour at 190–220° with four to six parts of quick-lime:

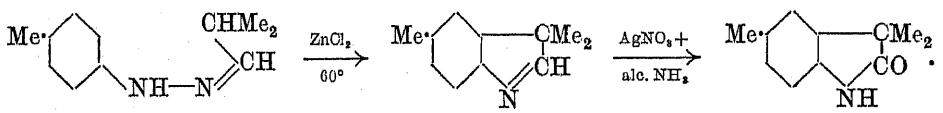


(80% yield.)

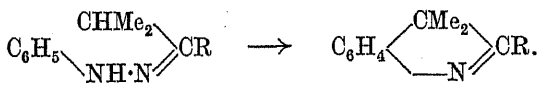
(R = Me, Et, Ph.)

The phenylhydrazide of acetoacetic acid (R = $\cdot COCH_3$) gives only a 4% yield. In D.R.-P. 218727 good yields are claimed when the sodio-derivative of the acid hydrazide is used.

In certain cases the Fischer reaction takes place with exceptional ease. Grgin [8] obtained 3 : 3 : 5-trimethylindolenine by warming the *p*-tolylhydrazone of *iso*butyraldehyde at 60° with alcoholic $ZnCl_2$:



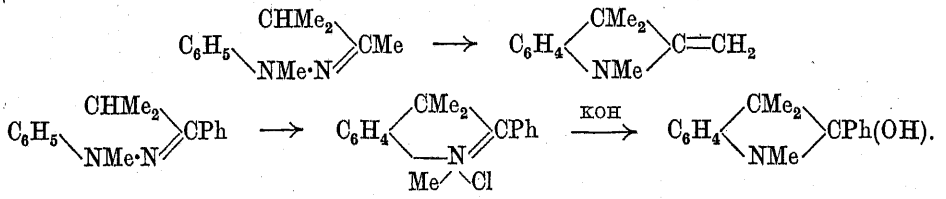
Plancher [9] had previously observed similar cases of easy ring-closure:



(R = Me or $\cdot CHMe_2$.)

[1] *J. Russ.*, 1913, **45**, 69, 70, 694.
[2] Nef, *Ann.*, 1891, **266**, 72; Walker, *Amer. Chem. J.*, 1893, **15**, 576; Reissert and Heller, *Ber.*, 1904, **37**, 4378.
[3] Wislicenus and Arnold, *Ann.*, 1888, **246**, 334.
[4] Plancher, *Ber.*, 1898, **31**, 1496, etc.
[5] Brunner, *Monatsh.*, 1896, **17**, 479; 1906, **27**, 1183, etc.
[6] D.R.-PP. 218477, 218727.
[7] *Monatsh.*, 1896, **17**, 479; 1897, **18**, 95, 527; 1906, **27**, 1183.
[8] *Ibid.*, p. 731.
[9] *Ber.*, 1898, **31**, 1496.

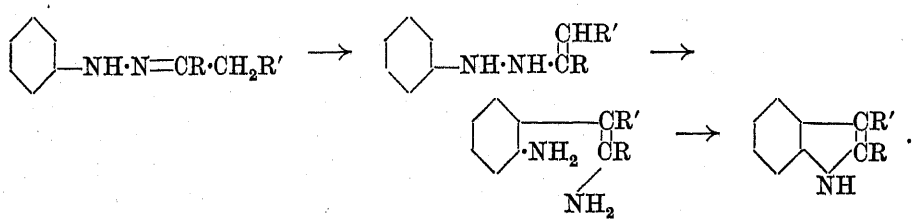
The methylphenylhydrazones of *iso*propyl methyl and phenyl ketones undergo ring-closure even at room temperature in the presence of alcoholic $ZnCl_2$: [1]



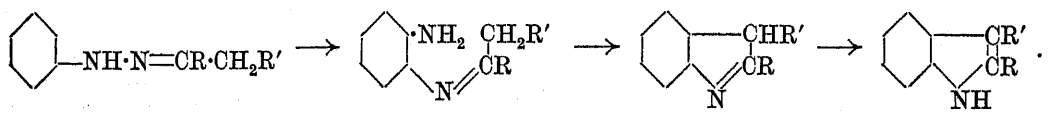
It will be observed that in each of these examples an *iso*propyl group, $\cdot CHMe_2$, is involved in the ring-closure.

For the mechanism of the Fischer synthesis, by which N, H_2 and H are removed as NH_3 from different parts of the hydrazone molecule, four suggestions have been made.*

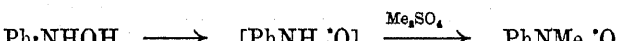
Robinson and Robinson [2] suppose that an unsaturated azine is first formed, which undergoes an *ortho* benzidine rearrangement and then loses NH_3 :



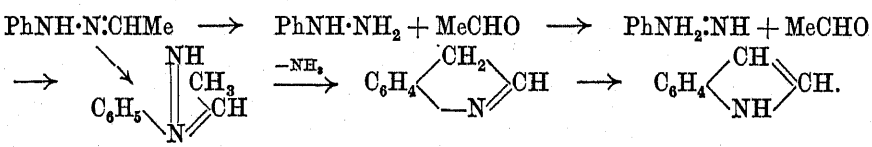
Cohn [3] has suggested an *ortho* semidine rearrangement (without previous conversion into azine), followed by elimination of NH_3 between the aromatic $\cdot NH_2$ group and $\cdot CH_2\cdot$:



Bamberger and Landau [4] suppose a tautomerism of the hydrazones of the same nature as that suggested for phenylhydroxylamine to explain the formation of dimethylaniline oxide on methylation with Me_2SO_4 :



The indole synthesis is figured thus :

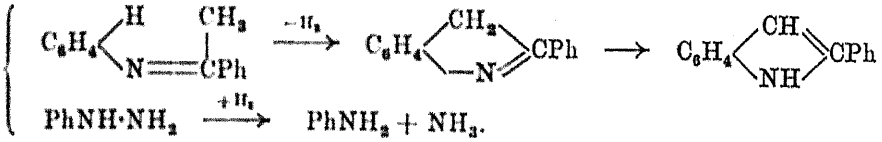


[1] Plancher, *loc. cit.*; Jennisch, *Monatsh.*, 1906, **27**, 1223.
[2] *J. C. S.*, 1918, **113**, 639.
[3] "Die Carbazolgruppe," 1919, p. 12.
[4] *Ber.*, 1919, **52**, 1097, footnote.

* For a discussion of these, see Hollins, *J. A. C. S.*, 1922, **44**, 1598; Robinson and Robinson, *J. C. S.*, 1924, **125**, 827.

Such an explanation would scarcely apply to methylphenylhydrazones, and the mechanism of the final elimination of NH_3 is by no means obvious. Moreover, the tautomery of phenylhydroxylamine, upon which the hypothesis rests, is quite unnecessary for the explanation of the formation of dimethylaniline oxide (as, indeed, is pointed out by Bamberger himself). Diazomethane gives no amine oxide, so that the evidence for the form $PhNH_2{:}O$ amounts to very little.

The most acceptable explanation of the Fischer synthesis is that advanced by Reddelien in 1912.[1] Reddelien discovered that acetophenone anil is oxidised by phenylhydrazine to 2-phenylindole, the phenylhydrazine being reduced in the process to ammonia and aniline :



Phenylhydrazones were found to have the same oxidising power, being themselves reduced to the ketone-imide and aniline. For the Fischer indole synthesis Reddelien therefore suggested the following stages :

(i) Reduction of the phenylhydrazone (during oxidation in (iii)) to aniline and ketone imide—

$$PhNH{\cdot}N{:}CR{\cdot}CH_2R + H_2 \longrightarrow PhNH_2 + NH{:}CR{\cdot}CH_2R.$$

(ii) Elimination of NH_3 between these two products—

$$PhNH_2 + NH{:}CR{\cdot}CH_2R \longrightarrow PhN{:}CR{\cdot}CH_2R + NH_3.$$

(iii) Ring-closure by oxidation by the phenylhydrazone—



(iv) Rearrangement of the resulting indolenine—

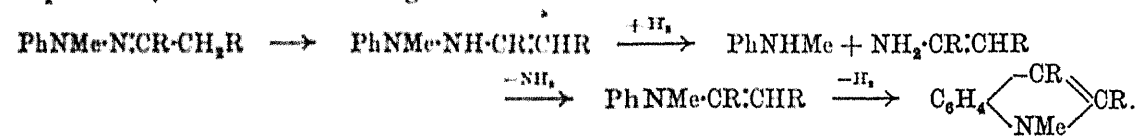


The easy conversion of the arylhydrazones of *iso*propyl ketones finds a satisfactory explanation here in the ready oxidisability of the group $\cdot CHMe_2$.

The theory as stated by Reddelien does not apply to *N*-substituted arylhydrazones, but a small modification removes this difficulty. It is only necessary to suppose that the imine formed in stage (i) isomerises to an unsaturated amine :

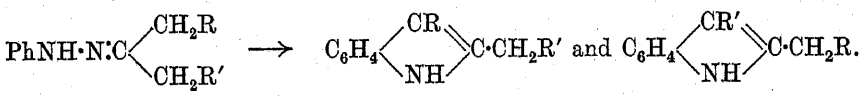
$$NH{:}CR{\cdot}CH_2R \longrightarrow NH_2{\cdot}CR{:}CHR,$$

or, alternatively, that the isomerisation occurs prior to stage (i) (as in Robinson and Robinson's explanation). The series of changes then becomes :

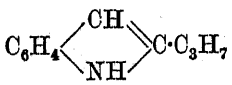


[1] *Ann.*, 1912, **388**, 179.

From the phenylhydrazone of an unsymmetrical ketone two isomeric indoles would be expected:



Only little work has been done to determine the course of the reaction in such cases. Methyl propyl ketone, $CH_3{\cdot}CO{\cdot}CH_2CH_2CH_3$, gives only 2-propylindole (I), but methyl *iso*propyl ketone, $CH_3{\cdot}CO{\cdot}CHMe_2$, owing to the reactivity of the *iso*propyl group, gives 2 : 3 : 3-trimethylindolenine (II):

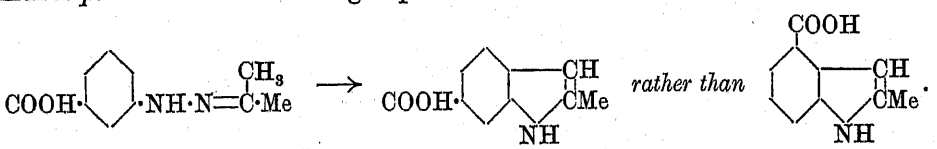


(I.)

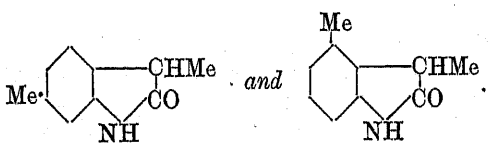


(II.)

Of the two *ortho* positions in *meta*-substituted phenylhydrazines the reactive one is probably that which is *para* to the substituent group: *



The *m*-tolylhydrazide of propionic acid is stated to give a mixture of the two possible oxindoles: [1]



On the other hand, the *m*-tolylhydrazide of β-phenylpropionic acid yields only a single product.[2]

Indoles have been prepared from the following arylhydrazones:

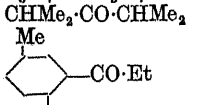
(*a*) *From phenylhydrazine:*

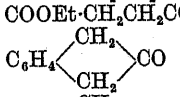
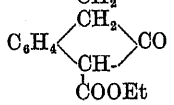
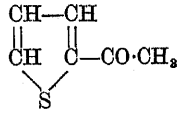
Aldehydes. R·CH₂·CHO	*References.*	*Aldehydes.*	*References.*
R = ·CH₃	5, 41	·C₆H₁₃	41
·C₂H₅	30, 41	·CHMe·COOH	28
·C₃H₇	41	·CH₂·COOMe	27
·CHMe₂	13	·CH₂CH₂NH₂	35
·C₄H₉	41	·CH₂Ph	41
·C₅H₁₁	13, 41	·C₆H₅	5, 14, 41

[1] D.R.-PP. 218477, 218727.

[2] Tomiček, *J. C. S.*, Abstr. 1922, i, 679.

* Borsche, (*Ann.*, 1908, **359**, 49–80) has demonstrated this in the analogous synthesis of tetrahydrocarbazoles (p. 169).

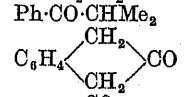
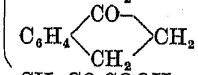
Ketones.	*References.*
$CH_3CO\cdot CH_3$	5, 41
$CH_3CO\cdot CH_2CH_3$	5, 21, 39
$CH_3CO\cdot CH_2Et$	5, 40
$CH_3CO\cdot CHMe_2$	25
$CH_3CO\cdot CH_2C_3H_7$	51
$CH_3CO\cdot CH_2CHMe_2$	51
$CH_3CO\cdot CH_2C_8H_{17}$	51
$CH_3CO\cdot CH_2COOEt$	16, 18, 41
$CH_3CO\cdot CH_2CH_2COOH$	5, 41
$CH_3CO\cdot CH_2Ph$	13
$CH_3CO\cdot CH_2CH_2Ph$	51
$CH_3CO\cdot COOH$	5, 41
$CH_3CO\cdot COOEt$	41
$CH_3CO\cdot Ph$	5, 14, 38, 41
$CH_3CO\cdot C_{10}H_7(\alpha\text{-})$	17
$C_3H_7\cdot CO\cdot C_3H_7$	40
$CHMe_2\cdot CO\cdot CHMe_2$	25
 (the free phenol fails)	48

Ketones.	*References.*
$PhCH_2\cdot CO\cdot CH_2Ph$	13
$PhCH_2\cdot CO\cdot Ph$	5, 41
$MeCH_2\cdot CO\cdot COOEt$	12
$COOH\cdot CH_2CH_2CO\cdot COOH$	36
$COOEt\cdot CH_2CH_2CO\cdot COOEt$	45
	46
	48
	17

(*b*) *From other primary hydrazines :*

Hydrazine.	*Aldehyde or ketone.*	*References.*
2 : 4-Dichlorophenylhydrazine	$CH_3\cdot CO\cdot CH_3$	44
p-Tolylhydrazine.	$CHMe_2\cdot CHO$	31
	$CH_3\cdot CO\cdot CH_3$	10, 41
	$CH_3\cdot CO\cdot COOH$	10
	$CH_3\cdot CO\cdot CH_2COOEt$	19
o-Tolylhydrazine.	$CH_3CO\cdot CH_2COOEt$	19
	$CH_3\cdot CO\cdot COOH$	10
m-Anisylhydrazine.	$COOH\cdot CH_2CH_2\cdot CO\cdot COOH$	45
p-Xylylhydrazine.	$CH_3\cdot CO\cdot COOH$	29, 41
m-Carboxyphenylhydrazine.	$CH_3\cdot CO\cdot CH_3$	7, 41
	$CH_3\cdot CO\cdot COOH$	7, 41
α-Naphthylhydrazine.	$CH_3\cdot CO\cdot CH_3$	11
	$CH_3\cdot CO\cdot COOH$	11
β-Naphthylhydrazine.	CH_3CHO	8
	$CH_3\cdot CO\cdot CH_3$	8, 41
	$PhCH_2\cdot CHO$	15
	$CH_3\cdot CO\cdot Ph$	15
	$CH_3\cdot CO\cdot COOH$	8
4 : 4′-Dihydrazinodiphenyl (from benzidine).	$CH_3\cdot CO\cdot CH_3$	41
	$CH_3\cdot CO\cdot COOH$	41

(*c*) *From* N-*substituted arylhydrazines :*

Hydrazine.	*Aldehyde or ketone.*	*References.*
PhNMe·NH_2	CH_3CH_2·CHO	6
	$PhCH_2$·CHO	15
	CH_3·CO·CH_3	6, 39, 41
	CH_3CH_2·CO·CH_3	6, 22
	$CHMe_2$·CO·CH_3	25
	C_4H_9·CO·CH_3	51
	$CHMe_2$·CH_2CO·CH_3	51
	n-C_9H_{19}·CO·CH_3	51
	COOH·CH_2CH_2·CO·CH_3	6
	COOH·CH_2·CO·CH_3	6
	CH_3·CO·COOH	1, 2, 24
	COOH·CH_2·CO·COOH	34
	COOEt·CHMe·CO·COOEt	45
	Ph·CO·CH_3	6, 41
	$PhCH_2CH_2$·CO·CH_3	51
	Ph·CO·$CHMe_2$	33
		46
		46
PhNR·NH_2	CH_3·CO·COOH	
R = methyl		1, 2, 24
ethyl		1, 2
propyl		24
benzyl		3
phenyl		9
PhNPh·NH_2	PhCO·CH_3	9
p-C_7H_7·NMe·NH_2	CH_3·CHO	37
	CH_3·CO·COOH	4
p-C_7H_7·NEt·NH_2	CH_3·CO·COOH	4
o-C_7H_7·NMe·NH_2	CH_3·CO·COOH	4
m-MeO·C_6H_4·NMe·NH_2	CH_3·CO·COOH	49

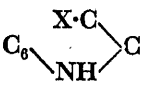
The following acid hydrazides have been converted into oxindoles :

Acid hydrazide.	*References.*
PhNH·NH·CO·CH_2R	
R = hydrogen	23
methyl	23, 42
ethyl	23
*iso*propyl	23, 26
benzyl	50
phenyl	23
PhNMe·NH·CO·CH_2R	
R = hydrogen	22
methyl	22
*iso*propyl	23, 26
benzyl	50
PhNH·NH·CO·$CHMe_2$	22
o-, *m*-, *p*-C_7H_7·NH·NH·CO·CH_2CH_2Ph	50
m-C_7H_7·NH·NH·CO·CH_2·CH_3	42
m-C_7H_7·NH·NH·CO·$CHMe_2$	23, 32

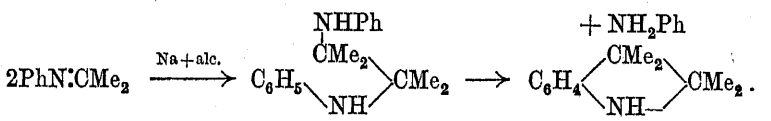
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References.

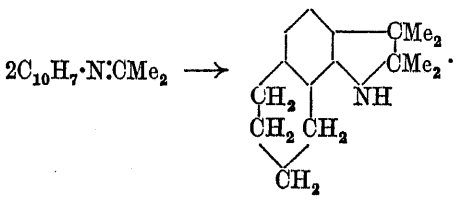
[1] Fischer and Jourdan, *Ber.*, 1883, **16**, 2245. [2] Fischer and Hess, *ibid.*, 1884, **17**, 559. [3] Antrick, *Ann.*, 1885, **227**, 260. [4] Hegel, *ibid.*, 1886, **232**, 214. [5] Fischer, *ibid.*, **236**, 126–145. [6] Degen, *ibid.*, pp. 153–163. [7] Roder, *ibid.*, pp. 164–173. [8] Schlieper, *ibid.*, pp. 174–184. [9] Pfülf, *ibid.*, 1887, **239**, 220. [10] Raschen, *ibid.*, p. 223. [11] Schlieper, *ibid.*, p. 229. [12] Wislicenus and Arnold, *ibid.*, 1888, **246**, 334. [13] Trenkler, *ibid.*, **248**, 106–113. [14] Fischer and Schmidt, *Ber.*, 1888, **21**, 1071, 1811. [15] Ince, *Ann.*, 1889, **253**, 38, 40, 42. [16] Nef, *ibid.*, 1891, **266**, 72. [17] Brunck, *ibid.*, 1893, **272**, 201–208. [18] Walker, *Amer. Chem. J.*, 1894, **16**, 430; Reissert and Heller, *Ber.*, 1904, **37**, 4378. [19] Walker, *Amer. Chem. J.*, 1894, **16**, 430. [20] Brunner, *Monatsh.*, 1894, **15**, 747. [21] *Idem*, *ibid.*, 1895, **16**, 183, 849. [22] *Idem*, *ibid.*, 1896, **17**, 253, 479. [23] *Idem*, *ibid.*, 1897, **18**, 95, 527–549. [24] Michaelis, *Ber.*, 1897, **30**, 2811, 2815. [25] Plancher, *ibid.*, 1898, **31**, 1496; *Gazz.*, 1898, **28**, ii, 418. [26] Schwarz, *Monatsh.*, 1903, **24**, 568. [27] Ellinger, *Ber.*, 1904, **37**, 1801. [28] *Idem*, *ibid.*, 1905, **38**, 2886. [29] Plancher and Caravaggi, *R. A. L.*, 1905, [v], **14**, i, 157. [30] Plancher and Carrasco, *ibid.*, ii, 31. [31] Grgin, *Monatsh.*, 1906, **27**, 731. [32] Brunner, *ibid.*, p. 1183. [33] Jennisch, *ibid.*, p. 1223. [34] Reif, *Ber.*, 1909, **42**, 3038. [35] Ewins, *J. C. S.*, 1911, **99**, 270. [36] Wislicenus and Waldmüller, *Ber.*, 1911, **44**, 1571. [37] v. Braun and Kruber, *ibid.*, 1912, **45**, 2977. [38] Reddelien, *Ann.*, 1912, **388**, 179. [39] Arbuzov and Tichvinski, *J. Russ.*, 1913, **45**, 69, 70. [40] *Idem*, *ibid.*, pp. 694, 697. [41] D.R.-P. 38784. [42] D.R.-PP. 218477, 218727. [43] D.R.-P. 238138. [44] Bülow, *Ber.*, 1918, **51**, 416. [45] Kermack, Perkin and Robinson, *J. C. S.*, 1921, **119**, 1622, 1636–9. [46] Armit and Robinson, *ibid.*, 1922, **121**, 837, 838. [47] v. Auwers, Hilliger and Wulf, *Ann.*, 1922, **429**, 222. [48] Perkin and Titley, *J. C. S.*, 1922, **121**, 1568. [49] Kermack, Perkin and Robinson, *ibid.*, p. 1880. [50] Tomiček, *J. C. S.*, Abstr. 1922, i, 679. [51] Kuroda, *J. Pharm. Soc. Japan*, 1923, 13–15, 131–142.

2. From acetone-anils: 

Knoevenagel [1] has shown that the reduction of acetone-anil with sodium and alcohol gives tetramethylindoline in almost quantitative yield:



Acetone-*p*-tolil behaves similarly, but the acetone compound of α-naphthylamine requires a higher temperature, and amyl alcohol must be used. The product is a tetrahydronaphthindoline:



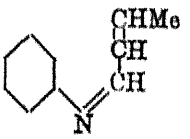
The formation of β-ethylindole by heating together aniline, lactic acid and zinc chloride [2]

[1] *Ber.*, 1922, **55**, 2309.

[2] Pictet and Duparc, *ibid.*, 1887, **20**, 3416.

is possibly due to the intermediate production of ethylidene-aniline, acetaldehyde being first formed from the lactic acid by loss of HCOOH (as CO and H_2O):

$$2PhN{:}CH{\cdot}CH_3 \longrightarrow PhN{:}CH{\cdot}CH{:}CHMe,\ i.e.$$



$\longrightarrow$



3. From oxanilide, etc.: $C_6{<}^{X.CO}_{N}{>}CO$

Bauer [1] obtained isatins by the action of conc. H_2SO_4 upon the dichloro-di-imides prepared from oxanilides, *e.g.*:

$$PhNH{\cdot}CO{\cdot}CO{\cdot}NHPh \xrightarrow{PCl_5} C_6H_5{<}^{ClC{:}NPh}_{N=C{\cdot}Cl} \xrightarrow{H_2SO_4} C_6H_4{<}^{CO}_{N=C{\cdot}OH}.$$

The yields are small except in the case of *o*-toluidine:

Amine.	*Yield of dichloro-di-imide.*	*Conversion into isatin.*	*Over-all yield of isatin.*
Aniline	70%	15%	10·5%
o-Toluidine	90	49	45
m-Toluidine	70	19	13
p-Toluidine	58	19	11
p-Anisidine	76·5	4	3
o-Anisidine	36	nil	nil

m-Toluidine gives only one isomeride, namely 6-methylisatin:

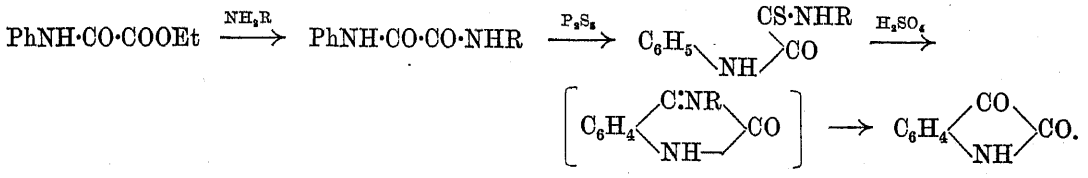


The method has been applied to the preparation of 7-bromoisatin from *o*-bromoaniline.[2]

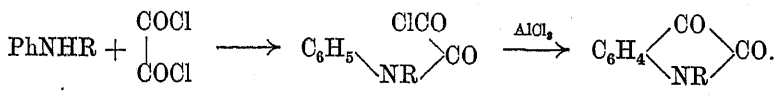
Phenyloxamic ester, PhNH·CO·COOEt, does not appear to undergo ring-closure,[3] but

[1] *Ber.*, 1907, **40**, 2650; 1909, **42**, 2111; D.R.-P. 193633.
[2] Friedländer, Bruckner and Deutsch, *Ann.*, 1912, **388**, 37.
[3] Schad, *Ber.*, 1893, **26**, 222.

Reissert [1] obtained a small yield from phenylthio-oxamide and a rather better one from the diphenyl derivative :



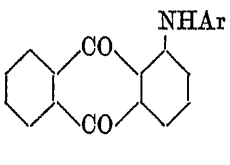
Much more satisfactory results were obtained by the action of oxalyl chloride upon secondary arylamines. This reaction was studied by Stollé,[2] who converted the resulting oxamic chlorides into isatins by the action of heat or of $AlCl_3$:



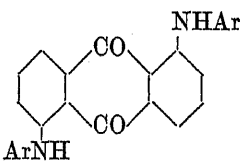
(R = methyl, ethyl, benzyl, phenyl, α- or β-naphthyl, anthraquinonyl, etc.)

The intermediate oxamic chloride need not in all cases be isolated; *e.g.* a mixture of ethylaniline, oxalyl chloride and $AlCl_3$ in CS_2 gives *N*-ethylisatin directly. Di-β-naphthyloxamic chloride undergoes cyclisation even in warm ether (without $AlCl_3$) and the diphenyl compound only requires a temperature of 100°.

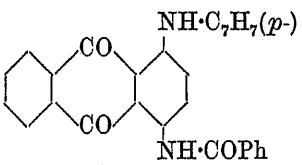
Various *N*-anthraquinonylisatins are described in the Bayer patent, D.R.-P. 286095, in which is mentioned the condensation of oxalyl chloride with the following compounds :



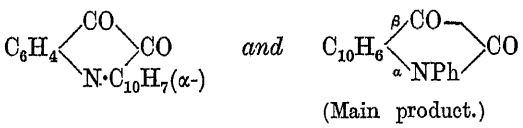
(Ar = Ph, *p*-C_7H_7.)



(Ar = *p*-C_7H_7, β-$C_{10}H_7$.)



From oxamic chlorides of the type $\frac{Ar}{Ar'}$>N·CO·COCl, where Ar and Ar′ are different aryl radicals, Stollé's method leads to two isomeric isatins. Thus [3] the oxamic chloride from phenyl-α-naphthylamine yields the two isatins :

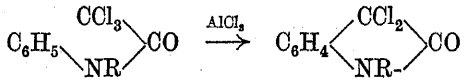


(Main product.)

[1] *Ber.*, 1904, **37**, 3724.
[2] *Ibid.*, 1913, **46**, 3915; *J. pr. Chem.*, 1922, **105**, 137; D.R.-PP. 281046, 282490, 335763; Staudinger, Swiss Pats. 92688, 93486–93489.
[3] Stollé, *J. pr. Chem.*, 1922, **105**, 137.

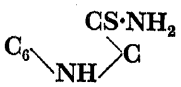
(no perinaphthisatin is formed). Only the naphthisatin results from phenyl-β-naphthylamine.

Trichloroacetyl chloride may be used in place of oxalyl chloride : [1]

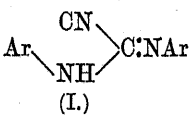


(R = methyl, ethyl, phenyl),

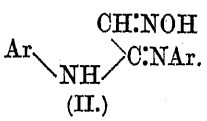
but dichloroacetyl derivatives of diphenylamine and methylamine fail to undergo ring-closure.

4. Sandmeyer's method from thiocarbanilide : 

The two Sandmeyer methods are closely related. In both an amidine is prepared—in the first, a cyanoformamidine * (I), and in the second an *iso*nitrosoacetamidine (II), which may be converted into the former by dehydration :



(I.)

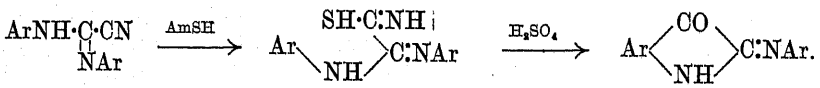


(II.)

The nitrile is obtained by the action of KCN and $PbCO_3$ upon thiocarbanilide or its homologues : [2]

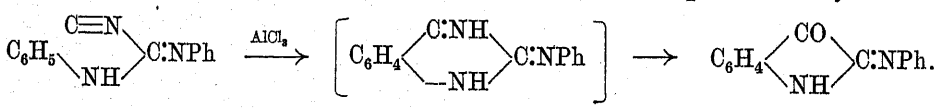


It is then treated with ammonium sulphide to give the thioamide,[3] from which an isatin-α-arylamide is obtained by the action of conc. $\cdot H_2SO_4$ [4] :



The indigo is then easily prepared by Bayer's method—reduction wth ammonium sulphide. [5]

An attempt to convert the nitrile directly into isatin by the action of conc. H_2SO_4 gave only a very small yield.[6] $AlCl_3$, however, brings about the ring-closure quite smoothly : [7]



[1] Stollé, *loc. cit.*, p. 147; D.R.-P. 341112.
[2] Sandmeyer, *Z. Farb. Text. Chem.*, 1903, **2**, 129; D.R.-PP. 115169, 116563, 264265.
[3] D.R.-PP. 113978, 115464. [4] D.R.-PP. 113980, 113981, 115465, 152019, 153418, 264265.
[5] D.R.-PP. 119280, 119831, 175423. [6] Schultz, Herzog and Rhode, *J. pr. Chem.*, 1906, **74**, 74, 76.
[7] D.R.-PP. 269750, 277396; Bonnefoy and Martinet, *Compt. rend.*, 1921, **172**, 220.
* This term seems preferable to the more usual "hydrocyancarbodiphenylimide."

The cyanoformamidines from *o*-, *m*-toluidines, *p*-chloroaniline, 6-chloro-*o*-toluidine and *β*-naphthylamine behave similarly.

The Sandmeyer method has been applied to thiocarbanilides derived from the following amines:

Aniline	D.R.-PP. 115169, 113978.
o-, *p*-Toluidines	D.R.-PP. 115464, 115465, 116563.
m-Toluidine	Bonnefoy and Martinet, *loc. cit.*
α-, *β*-Naphthylamines	D.R.-P.P. 152019, 153418.
1-Chloro-2-naphthylamine, 1-Bromo-2-naphthylamine	D.R.-P. 264265.

5. Sandmeyer's method from chloral, hydroxylamine and arylamines: $C_6<_{NH}^{CH:NOH}>C$

Sandmeyer in 1899[1] condensed together chloral hydrate, hydroxylamine and aniline and obtained *iso*nitrosoacetodiphenylamidine (I), which by the action of conc. H_2SO_4 was converted almost quantitatively into isatin-α-anilide (II):

$$2PhNH_2 + CCl_3\cdot CHO + NH_2OH \longrightarrow \underset{PhN}{\overset{PhNH}{>}}C\cdot CH:NOH \quad (I.)$$

$$C_6H_5<_{NH}^{CH:NOH}>C:NPh \xrightarrow{H_2SO_4} C_6H_4<_{NH}^{C:NH}>C:NPh \xrightarrow{H_2O} C_6H_4<_{NH}^{CO}>C:NPh.$$

(I.) (II.)

The yields are just as good when the hydroxylamine is replaced by its mono- or di-sulphonic acid (obtained by Raschig's method from $NaNO_2$ and $NaHSO_3$), though it is usual in this case to hydrolyse the sulphonic acid first to NH_2OH by boiling with dilute acid.[2]

The reaction has been further investigated by Martinet and Coisset,[3] who find that in neutral solution aniline reacts with chloral oxime to form the *iso*nitroso-amidine (III), but in dilute acid the product is *iso*nitroso-acetanilide (IV):

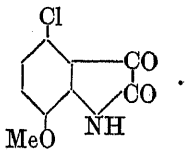
$$CCl_3\cdot CH:NOH + 2PhNH_2 \xrightarrow{\text{neutral}} \underset{PhN}{\overset{PhNH}{>}}C\cdot CH:NOH \quad (III.)$$

$$CCl_3\cdot CH:NOH + 2PhNH_2 \xrightarrow{\text{acid}} PhNH\cdot CO\cdot CH:NOH \quad (IV.)$$

On adding hydroxylamine hydrochloride and chloral hydrate to a boiling solution of 4-chloro-2-anisidine hydrochloride, Martinet and Coisset obtained after 5–10 minutes the *iso*nitrosoacetyl

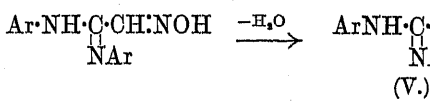
[1] D.R.-PP. 113848, 113981, 123887.
[2] D.R.-PP. 313725, 320647; Fr. Pat. 501153; Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234.
[3] *Compt. rend.*, 1921, **172**, 1234.

derivative of the base, and this was converted by conc. H_2SO_4 at 75° into the corresponding isatin :



The method is especially suitable for halogenated isatins, but fails with *p*-anisidine and *p*-phenetidine.[1]

The *iso*nitroso-amidines are readily dehydrated by P_2O_5 to give cyanoformamidines (V), from which isatins may be obtained by the methods described in the preceding section :



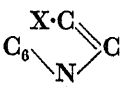
(V.)

Isatins have been prepared by the Sandmeyer chloral method from the following arylamines :

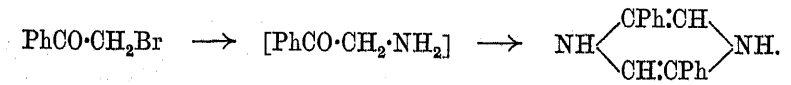
	References.		*References.*
Aniline.	1, 2, 3, 5	*p*-Bromoaniline.	4
o-Toluidine.	4	2 : 5-Dichloroaniline.	4
m-Toluidine.	4	2 : 4-Dibromoaniline.	4
p-Toluidine.	4	4-Chloro-*o*-anisidine.	4, 5
4-*m*-Xylidine.	4	3-Bromo-*p*-toluidine.	8
p-Xylidine.	4	Anthranilic acid.	4
o-Anisidine.	4	Methylaniline.	4
p-Phenetidine.	4, 7	Ethylaniline.	4
p-Chloroaniline.	4	Benzylaniline.	4
		4 : 4′-Diaminodiphenylmethane.	6

References.

[1] D.R.-PP. 113848, 113981, 123887. [2] Fr. Pat. 501153. [3] Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234. [4] D.R.-PP. 313725, 320647, E.P. 128122. [5] Martinet and Coisset, *Compt. rend.*, 1921, **172**, 1234. [6] Borsche and Meyer, *Ber.*, 1921, **54**, 2841. [7] Halberkann, *ibid.*, p. 3079. [8] Ressy and Ortodocsu, *Bull.*, 1923, [iv], **33**, 1297.

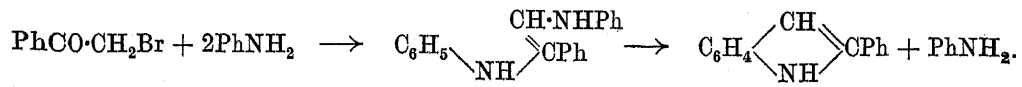
6. From *α*-halogenated ketones, etc., and arylamines : 

By the action of NH_3 upon phenacyl bromide, Staedel[2] obtained dihydrodiphenylpyrazine (" isoindole ") : [3]

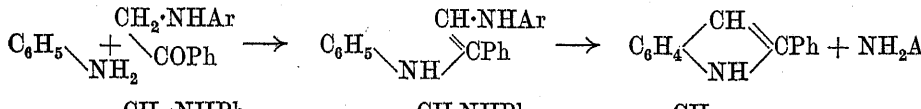


[1] Halberkann, *Ber.*, 1921, **54**, 3079. [2] *Ibid.*, 1880, **13**, 836.
[3] See V. Meyer and Treadwell, *ibid.*, 1883, **16**, 342.

Boiling aniline, however, behaves differently, giving "diphenyldiisoindole," [1] which was shown later to be α-phenylindole, not the β-isomeride, as might be expected.[2] This curious result was explained by Bischler: [3]

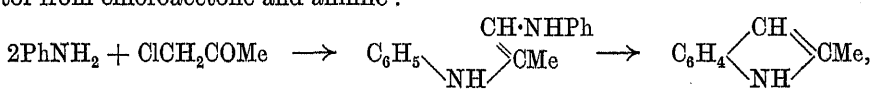


In accordance with this explanation, Bischler showed that phenacyl-arylamines when heated with aniline all gave the same α-phenylindole, while phenacylaniline heated with substituted anilines gave α-phenylindoles substituted in the nucleus:

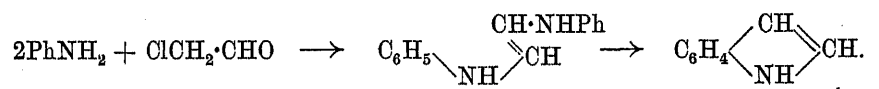


(Ar = *o*-, *m*-, *p*-tolyl, *m*-chlorophenyl.)

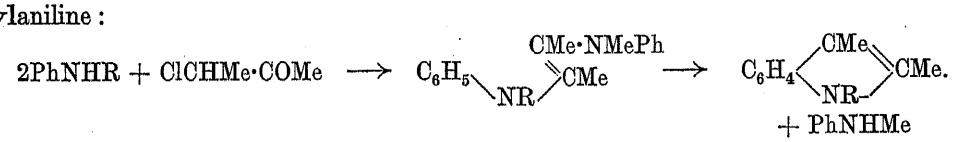
This view of the reaction brings it into line with Nencki and Berlinerblau's preparation [4] of methylketol from chloroacetone and aniline:



and with Berlinerblau's synthesis of indole by the action of aniline upon chloroacetaldehyde (or upon dichlorodiethyl ether, $ClCH_2{\cdot}CHCl{\cdot}OEt$, which readily hydrolyses to $ClCH_2{\cdot}CHO$): [5]



Vladesco [6] similarly obtained indoles from α-chloropropyl methyl ketone and aniline or methylaniline:



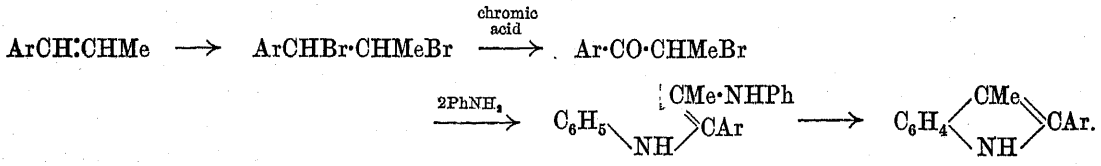
(R = H, Me.)

Vladesco's results were confirmed by Richard,[7] who was unable, however, to repeat the preparation of methylketol by Nencki and Berlinerblau's method from aniline and chloroacetone, the only product being phenylaminoacetone.

Phenylacyl bromide and methylaniline yield 1-methyl-2-phenylindole,[8] and the method has

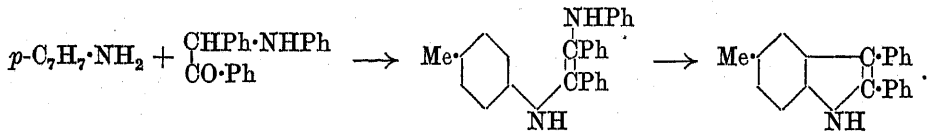
[1] Möhlau, *Ber.*, 1882, **15**, 2480.
[2] Wolff, *ibid.*, 1888, **21**, 123; Möhlau, *ibid.*, p. 510; Fischer and Schmidt, *ibid.*, pp. 1071, 1811.
[3] *Ibid.*, 1892, **25**, 2860. [4] *Ibid.*, 1887, **20**, Ref. 753; D.R.-P. 40889.
[5] *Monatsh.*, 1887, **8**, 180, 187; Wolff, *Ber.*, 1887, **20**, 427; 1888, **21** 123, 3360; D.R.-P. 40889.
[6] *Bull.*, 1892, [iii], **6**, 826. [7] *Compt. rend.*, 1907, **145**, 129. [8] Cullmann, *Ber.*, 1888, **21**, 2595.

been used by Hell and Bauer [1] for the preparation of methoxy- and ethoxy-arylindoles from anethole and eugenol ethyl ether :



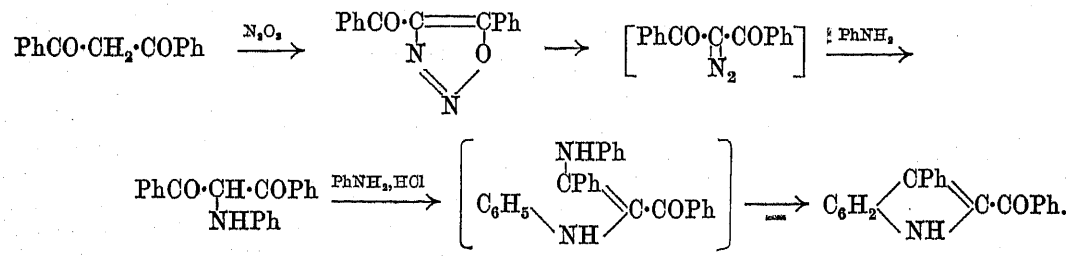
(Ar = *p*-anisyl or 4-ethoxy-3-methoxyphenyl.)

The anilides, toluidides, etc., obtained from benzoin are converted into indoles when heated with arylamine hydrochlorides : [2]



Naphthylamines in the same way give α- and β-naphthindoles.

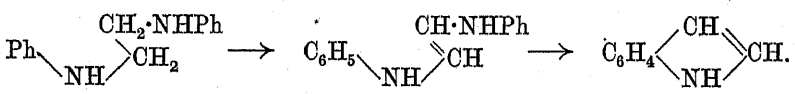
A very similar synthesis of 2-benzoyl-3-phenylindole is described by Wieland and Bloch : [3]



Wohl and Lange [4] failed to obtain indole from aniline and chloroacetal, the product being apparently a highly polymerised phenylaminoethylene :

$$PhNH_2 + ClCH_2{\cdot}CH(OEt)_2 \longrightarrow [PhNH{\cdot}CH{:}CH_2]_6.$$

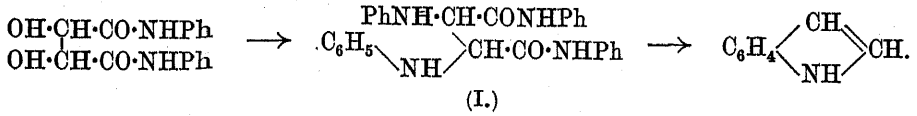
The formation of indole by the distillation with zinc dust of the oxidation product of ethylenediphenyldiamine [5] probably belongs to this type of synthesis :



The alkaline fusion of ethylenediphenyldiamine is said to yield indoxyl [6]

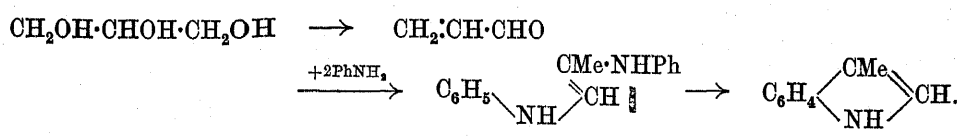
[1] *Ber.*, 1904, **37**, 866, 872.
[2] Bischler and Fireman, *ibid.*, 1893, **26**, 1336; Japp and Murray, *J. C. S.*, 1894, **65**, 889.
[3] *Ber.*, 1904, **37**, 1524; 1906, **39**, 1488.
[4] *Ibid.*, 1907, **40**, 4727.
[5] Prud'homme, *Bull.*, 1877, [ii], **28**, 558.
[6] D.R.-P. 220172.

Polikier [1] obtained indole in 6% yield by heating the dianilide of tartaric acid at 260–270°. Dianilinosuccinanilide (I) is first produced:

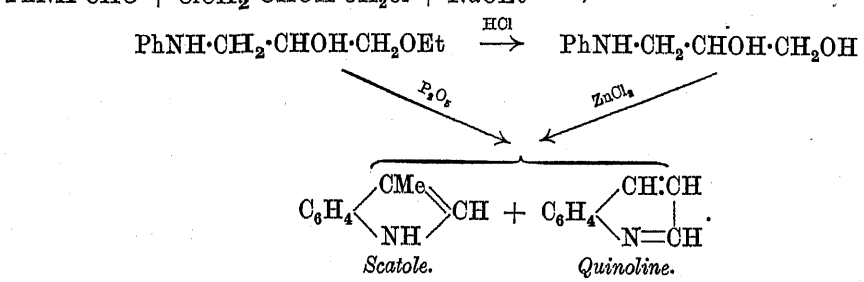


(I.)

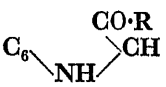
Scatole is produced by the action of $ZnCl_2$ upon a mixture of aniline and glycerol.[2] The reaction may be represented thus:



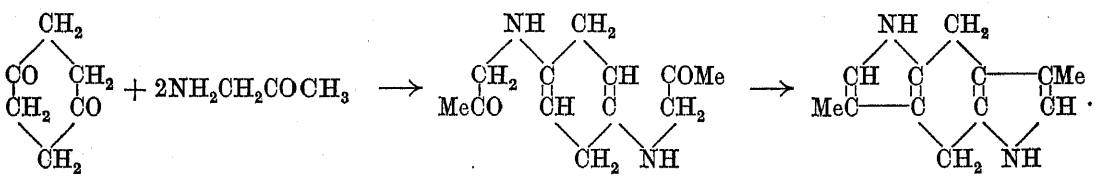
Bamberger and Kitschelt [3] observed a similar formation of scatole (and quinoline) from the compound $PhNH{\cdot}CH_2CHOH{\cdot}CH_2OEt$:



Scatole. *Quinoline.*

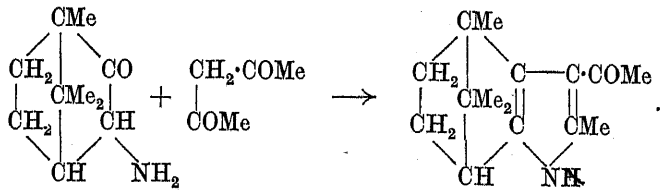
7. From cyclic ketones and aminoacetone, etc.: 

This extension of Knorr's pyrrole synthesis (p. 70) has been applied by Piloty [4] to the preparation of dimethyldihydropyrrindole from succinylsuccinic ester, which is converted during the reaction into dihydroquinol:

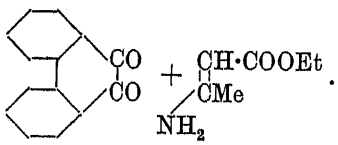


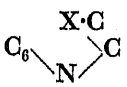
[1] *Ber.*, 1891, **24**, 2955.
[2] Fischer and German, *ibid.*, 1883, **16**, 710.
[3] *Ibid.*, 1894, **27**, 3421.
[4] *Ibid.*, 1910, **43**, 489.

α-Aminocamphor and acetylacetone were condensed together by Duden : [1]

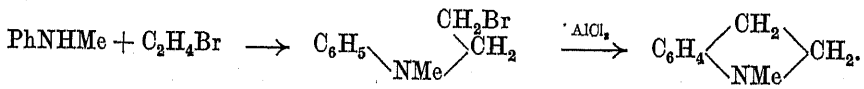


No indole derivative could be obtained by Feist and Stenger [2] from phenanthraquinone and β-aminocrotonic ester (*cf.* Pyrroles, p. 76) :

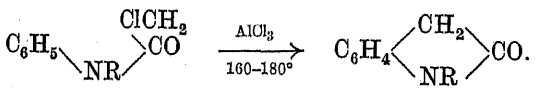


8. From chloroacetylated arylamines, etc. : 

β-Bromoethylmethylaniline gives only a poor yield of *N*-methylindoline when treated with aluminium chloride : [3]



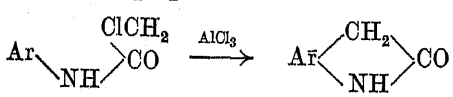
Much more satisfactory results are obtained with the chloroacetyl derivatives of secondary arylamines : [4]



(90–100% yield.)

(R = Me, Et, Ph.)

This method has been extended to the preparation of oxindoles from primary arylamines : [5]



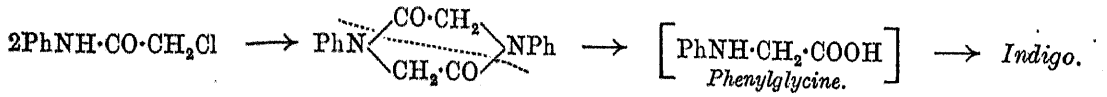
(Ar = phenyl, *o*- and *p*-tolyl.)

[1] *Ann.*, 1900, **313**, 25; *Ber.*, 1901, **34**, 3054. [2] *Ibid.*, 1902, **35**, 1561.
[3] v. Braun, Heider and Müller, *ibid.*, 1917, **50**, 1637; 1918, **51**, 273.
[4] Stollé, *ibid.*, 1914, **47**, 2120; D.R.-P. 335763. [5] *Idem*, *J. pr. Chem.*, 1922, **105**, 137.

It is not applicable to the primary naphthylamines, α-aminoanthraquinone or *m*-phenylenediamine. Chloroacetylbenzylaniline loses its benzyl group and gives oxindole.

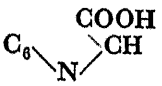
The preparation of 3 : 3-dichloro-oxindoles from trichloroacetyl derivatives has already been mentioned (p. 102).

Bromoacetanilide is converted into indigo by fusion with alkali.[1] In this case, however, the reaction proceeds *via* diphenyldiketopiperazine, which may be obtained from bromo- or chloroacetanilide by the action of alcoholic KOH and which yields indigo when fused with alkali : [2]

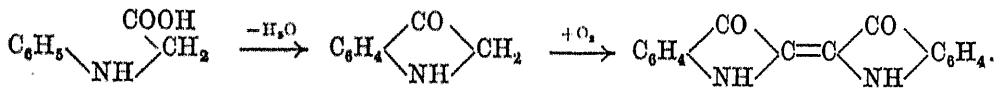


The chloroacetyl derivatives of *m*- and *p*-toluidines similarly give dimethylindigos.[3]

The chloroacetyl compounds for these syntheses are conveniently prepared by the action of a mixture of chloroacetic acid and thionyl chloride upon the base.[4]

9. From arylglycines : 

In Heumann's first synthesis of indigo [5] phenylglycine is melted with NaOH, giving indoxyl, which is converted by air oxidation into indigo :



From *o*-tolyl- and *m*-xylyl-glycines the corresponding methylated indigos are obtained,[6] but the reaction fails with *p*-tolylglycine.[7] The glycines from ethylaniline [8] and ethyl-*p*-toluidine [9] undergo ring-closure more easily than the non-alkylated substances, but the products are of no commercial interest.

The yield resulting from the ordinary melt with NaOH is small, and numerous modifications and additions have been suggested, generally with a view to eliminate the water formed in the reaction. Addition of sodium oxide,[10] sodium,[11] sodium hydride or amalgam,[12] sodium nitride,[13] sodium carbide,[14] calcium carbide [15] or magnesium [16] improves the yield. Anhydrous NaOH,[17] a mixture of NaOH, KOH and CaO,[18] NaOH with NaOEt [19] and NaOH with amyl alcohol [20] have also been used. The intimate mixture of the glycine and alkali obtained by

[1] Flimm, *Ber.*, 1890, **23**, 57.
[2] Kuhara and Chikashige, *J. C. S.*, Abstr. 1900, i, 560; *Amer. Chem. J.*, 1902, **27**, 1.
[3] *Idem, loc. cit.*; Eckenroth, *Ber.*, 1891, **24**, 698. [4] D.R.-P. 175586.
[5] Heumann, *Ber.*, 1890, **23**, 3043; Biedermann and Lepetit, *ibid.*, p. 3289; Lederer, *J. pr. Chem.*, 1890, **42**, 383, 565; 1891, **43**, 303; Heumann, *ibid.*, p. 111; D.R.-P. 54626.
[6] D.R.-PP. 58276, 61711, 61712. [7] Heumann, *Ber.*, 1891, **24**, 1346. [8] D.R.-P. 58276.
[9] D.R.-P. 63309. [10] D.R.-PP. 165691, 212845. [11] D.R.-PP. 189021, 215049.
[12] D.R.-PP. 163039, 166974, 166213. [13] D.R.-P. 166214. [14] Fr. Pat. 502836.
[15] D.R.-P. 166214. [16] D.R.-P. 195352. [17] D.R.-P. 179933.
[18] D.R.-P. 63310. [19] D.R.-P. 138903. [20] D. Pat. Anm. V 11014/1912.

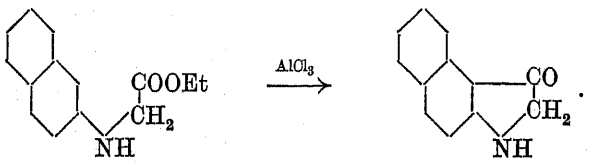
evaporating the aqueous solution *in vacuo*[1] also gives good results, but the best condensing agent is sodamide[2] or a mixture of sodamide and KCN. With this mixture even *p*-tolylglycine can be made to give a satisfactory yield of dimethylindigo. Modifications of the sodamide method are claimed in D.R.-PP. 166447, 179759 and Fr. Pats. 483836, 502837. Other sodio derivatives suggested are sodium cyanamide[3] and sodio-aniline.[4]

When the alkaline fusion is performed in the presence of only a limited amount of air the products are *leuco*-indigo and isatin.[5]

Phenylglycine may be replaced by the phosgenated derivative, $CO(NPh{\cdot}CH_2{\cdot}COOEt)_2$.[6]

The ring-closure may also be brought about by other methods. Phenylglycine is converted by oleum into an indigodisulphonic acid[7] and its *N*-alkylated derivatives behave similarly.[8] This method has been applied to *o*-, *m*- and *p*-chlorophenylglycines and to 2 : 4-dichlorophenylglycine by Schwalbe and Jochheim.[9]

$AlCl_3$ has been employed for the preparation of indoxyls from acetylphenylglycine[10] and *β*-naphthylglycine ester[11]:



β-Naphthindoxyl.]

For the manufacture of phenylglycines two methods are of technical importance. In the first of these, aniline (or its homologues) is condensed with chloroacetic acid[12]:

$$ArNH_2 + ClCH_2COOH \longrightarrow ArNH{\cdot}CH_2{\cdot}COOH,$$

or nitrobenzene etc., may be reduced with iron and chloroacetic acid.[13] Phenylglycine may also be obtained from its amyl ester by hydrolysis with aqueous KOH, the ester being prepared from amyl chloroacetate. The *ethyl* ester requires alcoholic KOH for its hydrolysis.

In the second commercial method for arylglycines, the arylamine is condensed first with formaldehyde and KCN,[14] or with formaldehyde-bisulphite and KCN[15] and the resulting arylaminoacetonitrile is hydrolysed with aqueous alkali[16]:

$$ArNH_2 + HCHO \longrightarrow ArNH{\cdot}CH_2OH \xrightarrow{KCN} ArNH{\cdot}CH_2{\cdot}CN \searrow ArNH{\cdot}CH_2{\cdot}COOH.$$

$$ArNH_2 + CH_2(OH){\cdot}SO_3Na \longrightarrow ArNHCH_2SO_3Na \xrightarrow{KCN} ArNHCH_2CN \nearrow$$

According to D.R.-P. 181723, phenylhydrazine may be used instead of aniline in the bisulphite

[1] D.R.-P. 152548. [2] D.R.-PP. 137955, 180394. [3] D. Pat. Anm. B 31030, B 41708/1908.
[4] D. Pat. Anm. B 41924. [5] D.R.-P. 105102. [6] D.R.-P. 123368.
[7] D.R.-P. 63218; Heymann, *Ber.*, 1891, **24**, 1476, 3066; Knietsch, *ibid.*, p. 2086; Vorländer and Schubert, *ibid.*, 1901, **34**, 1860. [8] D.R.-P. 68372.
[9] *Ibid.*, 1908, **41**, 3798. [10] D.R.-P. 188436. [11] D.R.-P. 216639.
[12] Wichelhaus, *Ber.*, 1893, **26**, 2547; D.R.-PP. 69636, 79861, 167698, 177491, 244603.
[13] D.R.-P. 175797. [14] D.R.-PP. 135332, 145376, 151538, 157617; D. Pat. Anm. F 15498.
[15] D.R.-PP. 132621, 156760. [16] D.R.-P. 169186.

method. The nitrile is also obtained by heating a mixture of aniline and formaldehydecyaohydrin on the water-bath : [1]

$$PhNH_2 + (OH)\cdot CH_2\cdot CN \longrightarrow PhNH\cdot CH_2\cdot CN.$$

Imbert [2] has patented the preparation of phenylglycine ester, together with a small amount of the anilide, by the condensation of aniline with dichlorovinyl ether :

$$ClCH{:}CCl\cdot OEt \longrightarrow ClCH_2\cdot COOEt \xrightarrow{PhNH_2} PhNH\cdot CH_2\cdot COOEt.$$

Phenyl- and tolyl-glycines are also formed by the reduction of the oxamic acids, $ArNH\cdot CO\cdot COOH$, with zinc dust and HCl.[3]

β-Hydroxyethyl-aniline, prepared from aniline and ethylene chlorohydrin, gives indoxyl when fused with alkali.[4] Phenylglycine is probably an intermediate stage :

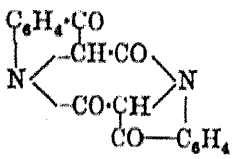
$$PhNH_2 + ClCH_2CH_2OH \longrightarrow PhNH\cdot CH_2CH_2OH \longrightarrow PhNH\cdot CH_2\cdot COOH \longrightarrow \textit{indoxyl.}$$

A similar oxidation to phenylglycine may account for the production of indoxyl by the alkaline fusion of ethylenediphenyldiamine, $PhNH\cdot CH_2\cdot CH_2\cdot NHPh$.[5]

Arylaminomalonic esters are converted by the action of heat into indoxylic esters [6] :

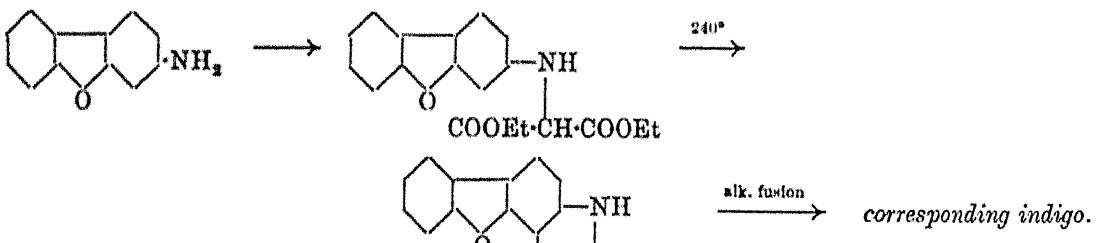
$$ArNH_2 + BrCH(COOEt)_2 \longrightarrow Ar{-}NH{-}CH(COOEt){\cdot}CH{\cdot}COOEt \longrightarrow Ar{<}\begin{matrix}CO\\NH\end{matrix}{>}CH\cdot COOEt.$$

In the case of phenylaminomalonic ester, a temperature of 260–265° is necessary; the *o*- and *p*-tolyl compounds undergo ring-closure at a somewhat lower temperature, the *m*-xylyl at 240° and the α- and β-naphthyl derivatives at 200°. Conrad and Reinbach [7] showed that diketopiperazines of the type



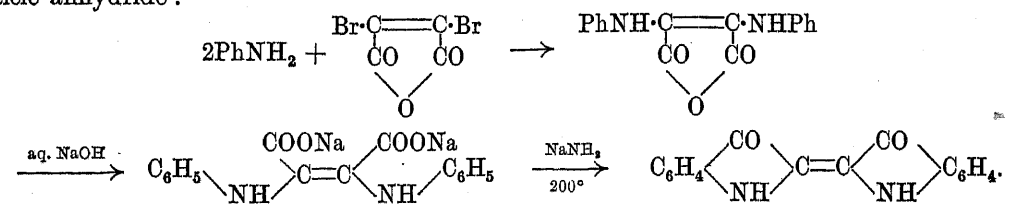
are formed as by-products. These may be converted into indoxylic acids by fusion with alkali at 250–280°.[8]

An indigo has recently been obtained from 2-aminodiphenylene oxide by the bromomalonic ester method [9] :

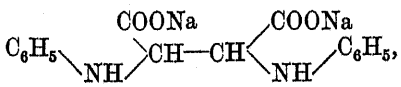


[1] D.R.-P. 138098. [2] D.R.-P. 199624; E.P. 13176/1907. [3] D.R.-P. 64909.
[4] D.R.-PP. 163043, 171172; E.P. 13956/1904. [5] D.R.-P. 220172.
[6] Blank, *Ber.*, 1896, **31**, 1812; D.R.-P. 109416. [7] *Ber.*, 1902, **35**, 523.
[8] D.R.-P. 129001. [9] Borsche and Schacke, *Ber.*, 1923, **56**, 2498.

A development from Heumann's synthesis which has additional interest now that benzene can be converted cheaply into maleic acid is the preparation of indigo from aniline and dibromomaleic anhydride : [1]

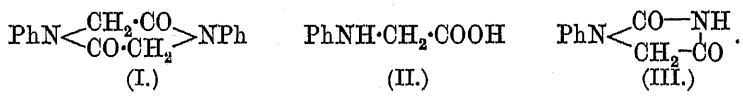


Vorländer [2] failed to obtain any trace of indigo by the alkaline fusion of the corresponding succinic derivative :



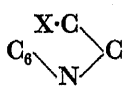
but the conversion has recently been found to proceed quite smoothly (60% yield) when NaOH, KOH and $NaNH_2$ are used in the presence of NH_3 at 230–240°.[3] The above intermediate is readily prepared from the dibromide of fumaric acid by the action of aniline.

N : *N*-Diphenyldiketopiperazine (I) as a source of phenylglycine (II) has already been mentioned (p. 109). Another compound closely related to phenylglycine is 1-phenylhydantoin (III) :

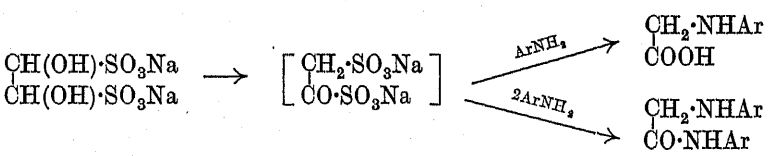


Phenyl- and *o*-tolyl-hydantoins give the corresponding indigos when fused with alkali, barium oxide [4] and sodamide [5] being especially suitable.

A 5 : 5′-*bis*indigo has been obtained from benzidine by the chloroacetic acid method.[6]

10. From arylamines and glyoxal-bisulphite : 

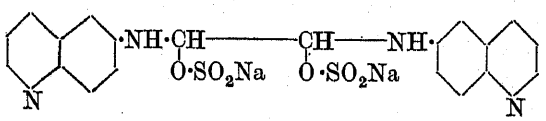
In Hinsberg's synthesis an arylamine is condensed with a hot aqueous-alcoholic solution of glyoxal-bisulphite. Primary amines of the benzene series are converted into a mixture of arylglycine and the corresponding arylamide, the latter being usually the main product * :



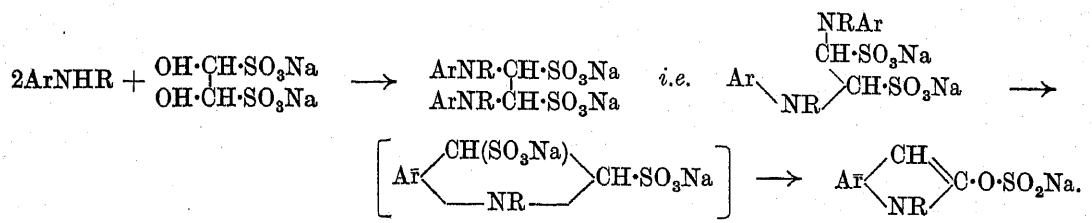
[1] Salmony and Simonis, *Ber.*, 1905, **38**, 2600.
[2] *Ibid.*, 1894, **27**, 1604.
[3] Bailey and Potter, *J. A. C. S.*, 1922, **44**, 215.
[4] D.R.-P. 142700.
[5] D.R.-P. 132477.
[6] D.R.-P. 300094.

* Both may, of course, be converted into indigos by alkaline fusion (preceding section).

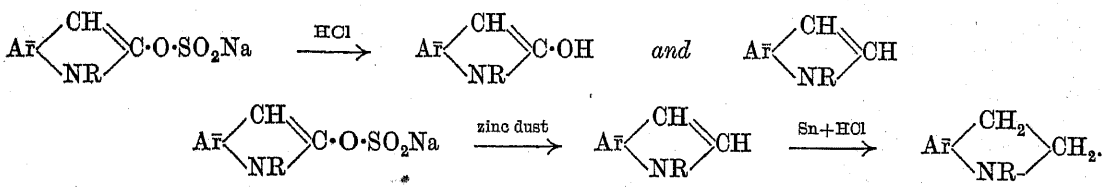
Piperidine behaves similarly, but 6-aminoquinoline gives only a diaminoethane derivative [1]:



With secondary amines of the benzene series and with all naphthylamine derivatives ring-closure occurs and an oxindole sulphurous ester is formed:



The products may be converted into oxindoles (with a small proportion of indoles) by warming with HCl at 80–90°, into indoles by distillation with zinc dust and into dihydroindoles by reduction with Sn and HCl:



The oxindole sulphurous esters are in every case accompanied by a small amount of the glycine-amide formed as mentioned above.

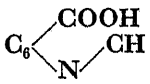
The reaction has been applied to the following arylamines:

(a) *Giving only glycines and glycine-amides.*	*References.*	(b) *Giving oxindole derivatives.*	*References.*
Aniline.	1, 6	Methylaniline.	3
o-Toluidine.	3	Ethylaniline.	3
p-Toluidine.	1	Methyl-*p*-phenetidine.	6
(Benzylamine.)	2	α-Naphthylamine.	1
p-Aminophenol.	6	β-Naphthylamine.	1, 4
p-Aminodimethylaniline.	6	1 : 8-Naphthylaminesulphonic acid ("Peri-acid").	5
Piperidine.	3	Methyl-β-naphthylamine.	6
		Ethyl-β-naphthylamine.	2, 3

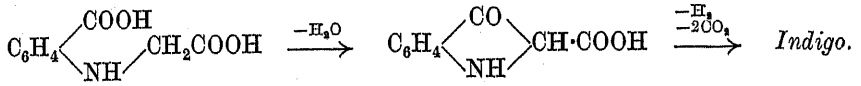
References.

[1] Hinsberg, *Ber.*, 1888, **21**, 110. [2] *Idem*, *ibid.*, 1892, **25**, 2545. [3] Hinsberg and Rosenzweig, *ibid.*, 1894, **27**, 3253. [4] Hinsberg and Simcoff, *ibid.*, 1898, **31**, 251. [5] Pschorr and Kuhtz, *ibid.*, 1905, **38**, 219. [6] Pschorr and Karo, *ibid.*, 1906, **39**, 3142. [7] Hinsberg, *ibid.*, 1908, **41**, 1367.

[1] Hinsberg, *Ber.*, 1908, **41**, 1372.

11. From *o*-carboxyphenylglycines, etc.: 

In Heumann's second synthesis of indigo [1] phenylglycine-*o*-carboxylic acid is fused with alkali to give indoxylic acid, which is converted by air oxidation into indigo:



The anilide, $COOH{\cdot}C_6H_4{\cdot}NH{\cdot}CH_2{\cdot}CONHPh$,[2] or the acetylated ester:

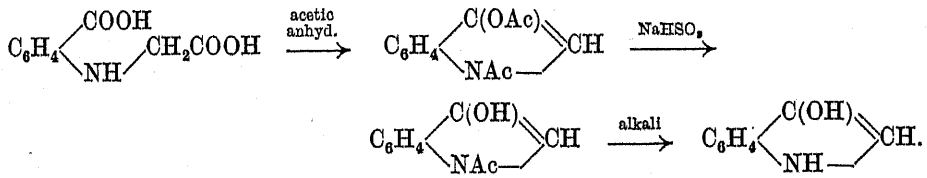
$$COOH{\cdot}C_6H_4{\cdot}NAc{\cdot}CH_2{\cdot}COOEt,^{3}$$

may be used instead of the free acid or its salts.

When the melt is carried out at 280–300° a mixture of indigo with about 20% of indole results.[4]

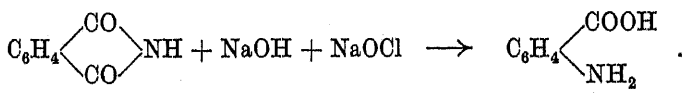
The ester, $COOEt{\cdot}C_6H_4{\cdot}NH{\cdot}CH_2{\cdot}COOEt$, or its acetyl derivative is converted into indoxylic ester by treatment with Na or NaOEt,[5] with sodium amyl oxide [6] or with sodioacetanilide.[7] This reaction has been studied by Vorländer and Schilling.[8] The acetylated ester gives *leuco*indigo when warmed with 20% NaOH at 100°, ring-closure being apparently facilitated by the acetylation of the $\cdot NH_2$ group.[9]

Excellent yields of the *O*-acetate of *N*-acetylindoxyl are obtained by the action of acetic anhydride upon phenylglycine-*o*-carboxylic acid,[10] or its mono- and di-ethyl esters.[11] The *O*-acetyl group may be eliminated by treatment with $NaHSO_3$ or Na_2HPO_4 solution,[12] or both acetyl groups with hot aqueous alkali:



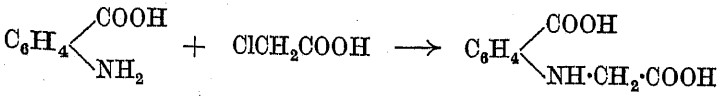
The ring-closure may also be brought about by heating the phenylglycinecarboxylic acid or its esters, amides or anilides in glycerol, lactic acid or other high-boiling hydroxylated compounds.[13]

For the preparation of phenylglycine-*o*-carboxylic acid anthranilic acid is the starting material. This can be made fairly cheaply from phthalimide by the Hofmann reaction:

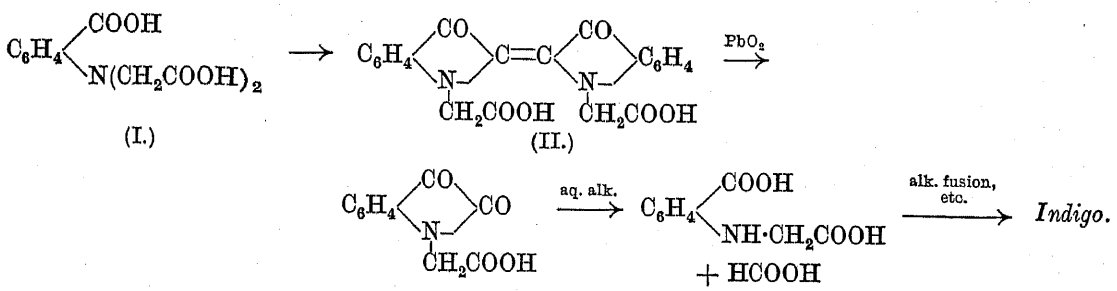


[1] *Ber.*, 1890, **23**, 3431; D.R.-PP. 56273, 85071, 85494, 142700, 152548, 232986; Vorländer and v. Pfeiffer, *Ber.*, 1919, **52**, 325.
[2] D.R.-P. 153577.
[3] D.R.-P. 138177.
[4] D.R.-P. 152683.
[5] D.R.-PP. 105495, 126962.
[6] D. Pat. Anm. F. 12903.
[7] D.R.-P. 158089.
[8] *Ann.*, 1898, **301**, 349.
[9] Vorländer, *Ber.*, 1902, **35**, 1683; Vorländer and Weissbrenner, *ibid.*, 1900, **33**, 556; D. Pat. Anm. F. 10983.
[10] D.R.-P. 113240.
[11] D.R.-P. 120321.
[12] D.R.-P. 108761.
[13] D.R.-P. 135638.

Anthranilic acid may be condensed with chloroacetic acid or ester [1] as in the preparation of phenylglycine:

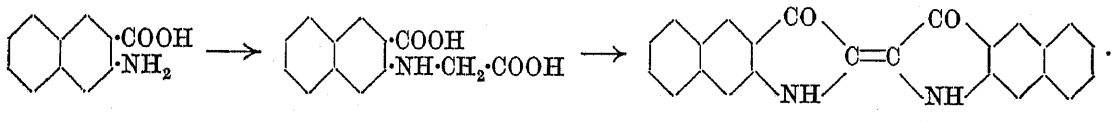


There is formed at the same time an appreciable amount of the tertiary amine (I), which by alkaline fusion is converted into indigodiacetic acid (II).[2] This is worthless as a dyestuff, but may be made to give indigo by oxidation followed by hydrolysis and alkaline fusion: [3]

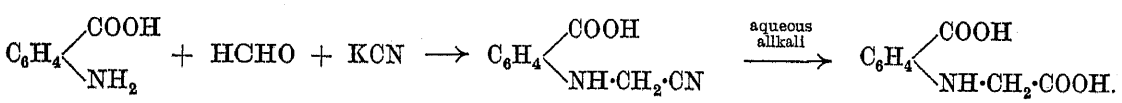


Vorländer and Mumme [4] have converted indigodiacetic acid (II) into *N* : *N*-dimethylindigo by removal of CO_2.

The chloroacetic acid method has also been used by Fierz and Tobler [5] for the preparation of linear *β*-naphthindigo from 3-amino-2-naphthoic acid:



Phenylglycine-*o*-carboxylic acid is also prepared by the formaldehyde methods, with or without bisulphite: [6]



Tetrabromophenylglycinecarboxylic acid obtained by this method was converted into octa bromoindigo by Grandmougin.[7]

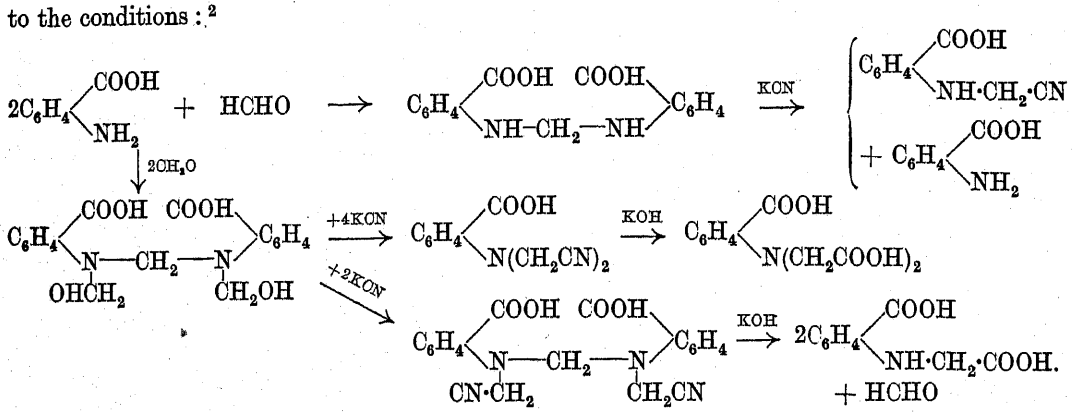
Heller and Fiesselmann [8] have shown that when anthranilic acid is treated with formaldehyde,*

[1] D.R.-PP. 127178, 122687. [2] D.R.-P. 128955. [3] D.R.-P. 168292.
[4] *Ber.*, 1900, **33**, 3182; 1902, **35**, 1699. [5] *Helv. Chim. Acta*, 1922, **5**, 558.
[6] D.R.-PP. 117924, 120105, 123695, 132621, 138098, 157710, 158346, 216748.
[7] *Compt. rend.*, 1921, 173, 982. [8] *Ann.*, 1902, **324**, 118.

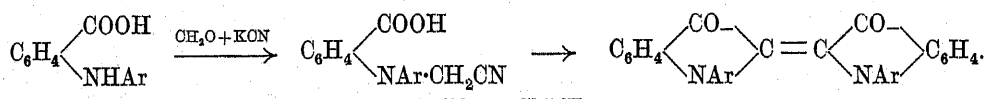
* The more commonly accepted structure for the formaldehyde compound of anthranilic acid is (III), *i.e.* the anhydro derivative of the primary condensation product (IV)



the product is not $COOH{\cdot}C_6H_4{\cdot}N{:}CH_2$,[1] but methylene-dianthranilic acid, $CH_2(NH{\cdot}C_6H_4{\cdot}COOH)_2$. This is attacked even in the cold by aqueous KCN solution; the products obtained vary according to the conditions:[2]



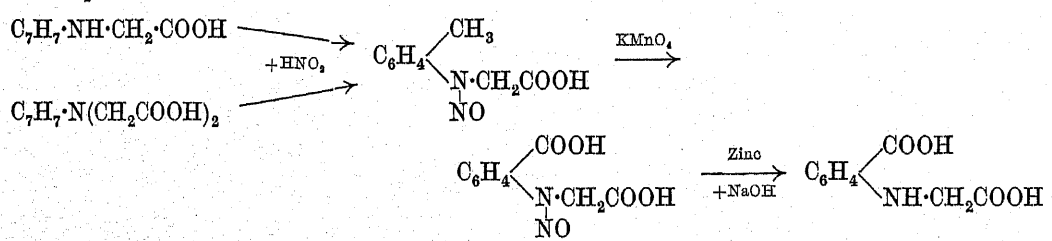
The conversion of the nitrile into ester is described in D.R.-PP. 120138, 129375, 129562, 136779. The method has been applied to the preparation of *N* : *N*-diarylindigos from phenyl- and *p*-chlorophenyl-anthranilic acids by Friedländer and Kunz:[3]



(Ar = Ph, *p*-ClC_6H_4.)

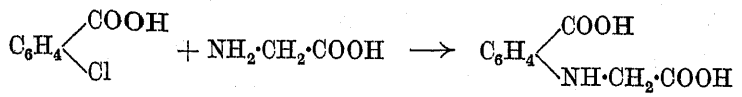
Indoxyl (and in some cases *leuco*indigo) has also been obtained in moderate yield by the alkaline fusion of anthranilic acid with such hydroxylated substances as glycerol, mannitol, starch, cellulose,[4] or glucose.[5] Glucose is said to give an 80% yield of indigo. The mechanism of the reaction has been discussed by Ostromisslensky and Pamfilov.[6] The alkali acts as a true oxidising agent and the primary condensation product is converted into phenylglycine-*o*-carboxylic acid. The $\cdot CH_2OH$ group of *o*-aminobenzyl alcohol is similarly oxidised to $\cdot COOH$ when this substance is heated with glycerol and KOH at 280–300° even in an atmosphere of nitrogen.

p-Toluidine is no longer employed for the manufacture of phenylglycine-*o*-carboxylic acid. It was formerly condensed with chloroacetic acid (or ester), nitrosated, and finally oxidised with $KMnO_4$:[7]

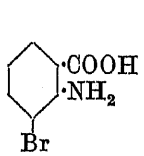


[1] As suggested by Miller and Plöchl, *Ber.*, 1892, **25**, 2020, and in D.R.-PP. 117924, 158346.
[2] D.R.-P. 216749.
[3] *Ber.*, 1922, **55**, 1598.
[4] D.R.-PP. 105569, 109319, 111067; Voswinkel, *Zentr.*, 1899, ii, 481.
[5] D.R.-P. 217945.
[6] *J. C. S.*, Abstr. 1909, i, 838.
[7] D.R.-PP. 121287, 127577, 135564, 138845; Vorländer and Schilling, *Ber.*, 1901, **34**, 1646.

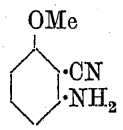
o-Chlorobenzoic acid, a by-product in the preparation of *o*-chlorobenzaldehyde, condenses with glycine to give phenylglycine-*o*-carboxylic acid:[1]



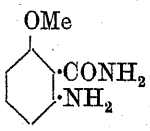
No arylglycine-*o*-carboxylic acid is obtainable from 3-bromoanthranilic acid (V) either by the chloroacetic acid method or by means of formaldehyde and KCN.[2] The 7 : 7′-dibromoindigo was eventually prepared from *o*-bromoaniline by Bauer's method (p. 100).



(V.)



(VI.)



(VII.)

o-Cyano-*m*-anisidine (VI) also refused to condense with chloroacetic acid, though the corresponding amide (VII) reacted easily.

The chloroacetic acid method or the formaldehyde method has been used for the preparation of indoxylic acids and indigos from the following *substituted* anthranilic acids.*

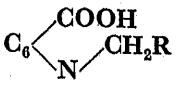
Anthranilic acid substituent.†	*References.*	*Anthranilic acid substituent.*	*References.*
N-Phenyl-	12	3-Chloro-5-bromo-	9
N-*p*-Chlorophenyl-	12	3-Bromo-5-chloro-	9
(*N*-Acetic acid.)	3	Tetrachloro-	8
5-Chloro-	4	5-Sulpho-	5, 6
4-Bromo-	11	4-Nitro-	10
5-Bromo-	11	4-Methoxy-	11
6-Bromo-	11	6-Methoxy-	11
5 : 6-Dichloro-	7	4-Ethoxy-	11
3 : 5-Dichloro-	9	4-Hydroxy*iso*propyl-	14
4 : 6-Dibromo-	8	5-Carboxy-	2
		6-Carboxy-	1
		[3-Amino-2-naphthoic acid	13]

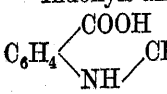
References.

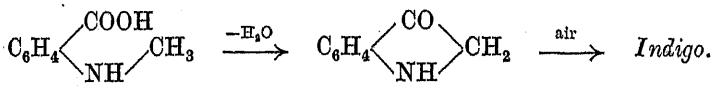
[1] D.R.-P. 73687. [2] D.R.-P. 113240. [3] D.R.-P. 128955. [4] D.R.-P. 135638. [5] D.R.-P. 143141. [6] D.R.-P. 154524. [7] D.R.-P. 216749. [8] D.R.-P. 220839. [9] D.R.-P. 226689. [10] Schwarz, *Monatsh.*, 1905, **26**, 1253. [11] Friedländer, Bruckner and Deutsch, *Ann.*, 1912, **388**, 23. [12] Friedländer and Kunz, *Ber.*, 1922, **55**, 1598. [13] Fierz and Tobler, *Helv. Chim. Acta*, 1922, **5**, 558. [14] Phillips, *J. A. C. S.*, 1902, **44**, 1775.

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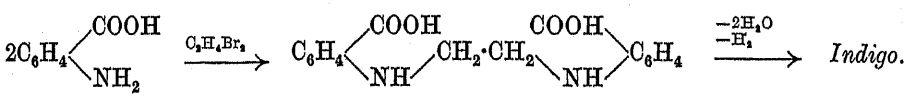
[1] D.R.-PP. 120900, 125456, 142506, 142507, 143902.
[2] Friedländer, Bruckner and Deutsch, *Ann.*, 1912, **388**, 37.
* For references to indigo itself from anthranilic acid, see the preceding pages.
† "·COOH = 1, ·NH_2 = 2."

12. From *N*-substituted anthranilic acids (other than glycines): 

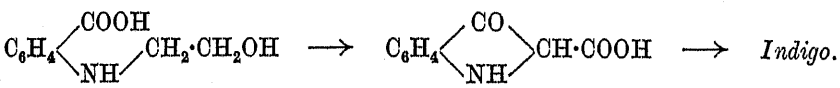
Indoxyls and indigos may also be obtained by the alkaline fusion of compounds of the type  , in which R is other than ·COOH. The simplest case is methylanthranilic acid [1] or its formyl derivative: [2]



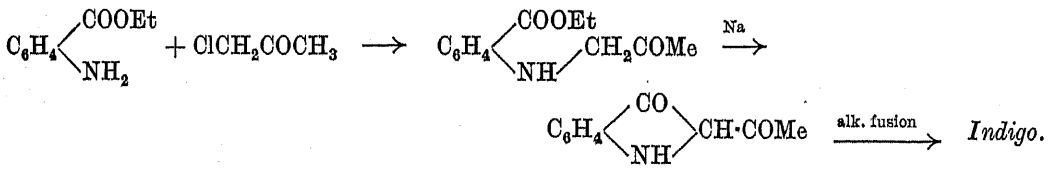
Ethylenedianthranilic acid in the same way gives indigo directly [3]:



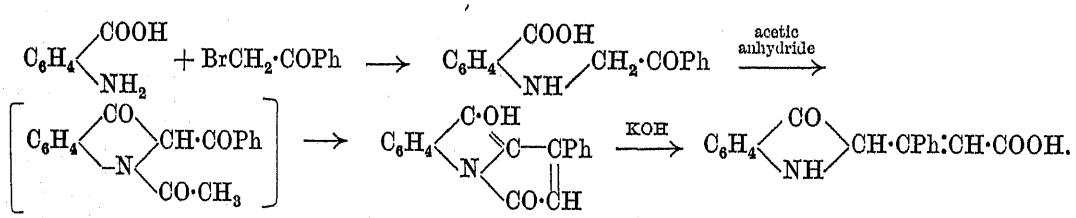
β-Hydroxyethylanthranilic acid, from anthranilic acid and ethylene chlorohydrin, yields indigo when fused with alkali: [4]



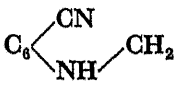
Chloroacetone may be used in place of the ethylene chlorohydrin: [5]



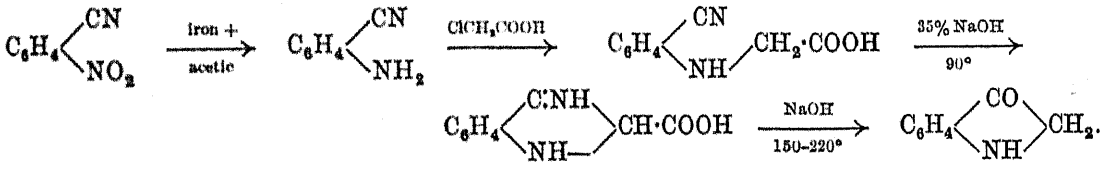
Scholtz [6] has obtained an interesting indole derivative from phenacylanthranilic acid by the action of acetic anhydride:

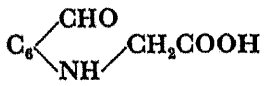


[1] D.R.-PP. 79409, 137208.
[2] D.R.-PP. 139393, 145601.
[3] Frankel and Spiro, *Ber.*, 1895, **28**, 1685; D.R.-P. 83056.
[4] D.R.-P. 163043.
[5] D.R.-P. 111890.
[6] *Ber.*, 1918, **51**, 1645.

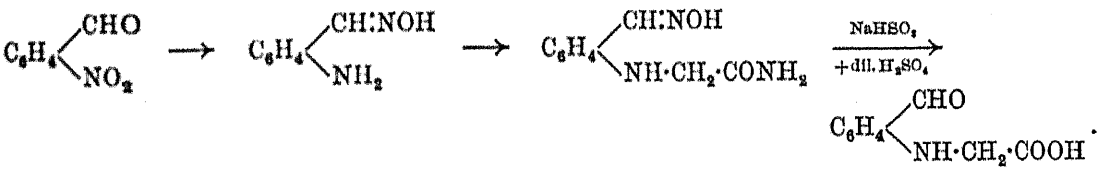
13. From *o*-cyanophenylglycine: 

Indoxyl has been prepared by the action of 35% NaOH at 90° upon *o*-cyanophenylglycine, followed by alkaline fusion at 150–220° : [1]

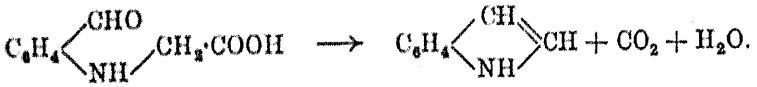


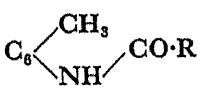
14. From *o*-aldehydophenylglycine: 

Gluud [2] prepared *o*-aldehydophenylglycine by the following series of reactions :

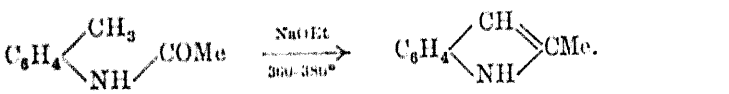


It is converted into indole (80% yield) by heating it with acetic anhydride and sodium acetate [3] :



15. From acylated *o*-toluidines (Madelung's method): 

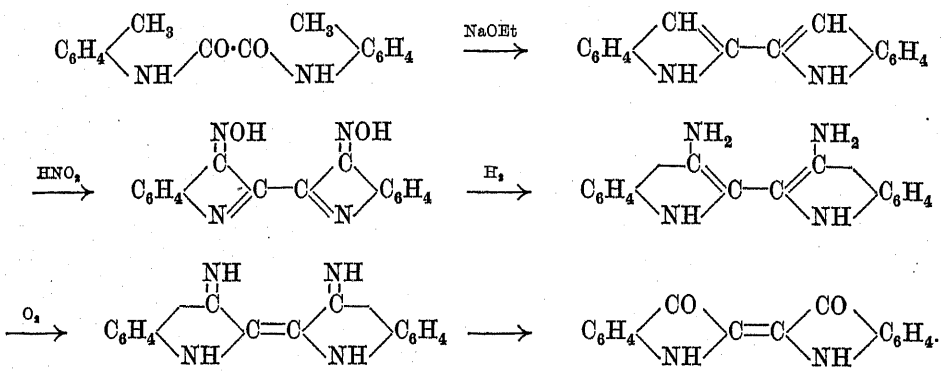
Mauthner and Suida [4] obtained very small yields of methyl indoles by distilling *o*-acetotoluidine with zinc dust. Madelung,[5] by using NaOEt or fused baryta in a current of hydrogen at 360–380°, improved the yield to 60% :



[1] D.R.-P. 206903.
[2] *J. C. S.*, 1913, **103**, 1254.
[3] Gluud, *Ber.*, 1915, **48**, 420; D.R.-P. 286761.
[4] *Monatsh.*, 1886, **7**, 230, 237.
[5] D.R.-P. 262327; *Ber.*, 1912, **45**, 1128, 3521; *Ann.*, 1914, **404**, 1; **405**, 58.

The reaction fails with formyl-*o*-toluidine, but gives a good yield with acetyl- and benzoyl-compounds, especially when sodium amyloxide is used as condensing agent. Salway [1] has used this method for the synthesis of substances allied to physostigmine.

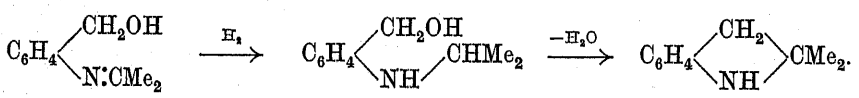
From oxal-*o*-toluidide Madelung prepared di-indyl in 26% yield. The di-*iso*nitroso derivative on reduction gives a diamine which is converted into indigo by oxidation and hydrolysis :



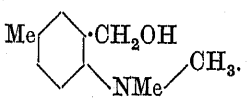
Acetyl-4-*m*-xylidine gives 2 : 5-dimethylindole.[2]

16. From *iso*propylaminobenzyl alcohol: $C_6\langle^{CH_2X}_{NH}\rangle CH$

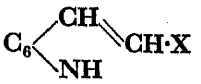
By dehydration of *iso*propylaminobenzyl alcohol Paal and Laudenheimer [3] prepared 2 : 2-dimethyldihydroindole :



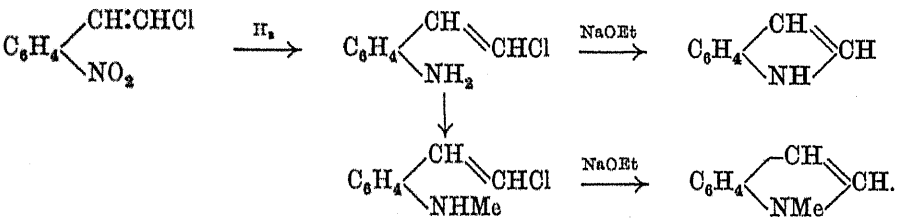
The closing of the ring in this manner seems to be due to the reactivity of the tertiary hydrogen of the ·$CHMe_2$ group, for no indole was obtained by v. Braun and Kruber [4] from



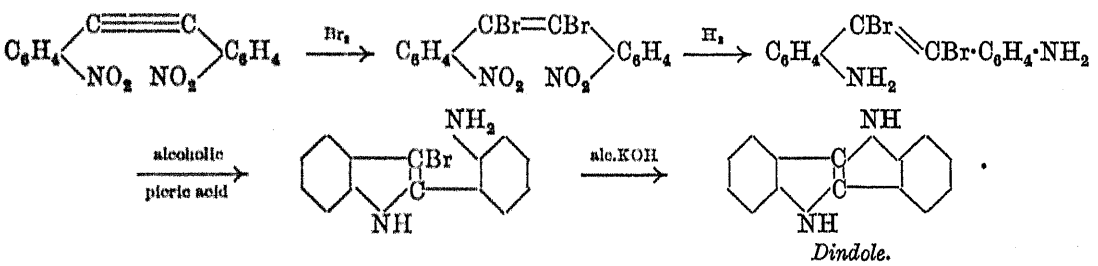
[1] *J. C. S.*, 1913, **103**, 351.
[2] Salway, *ibid.*, p. 1990.
[3] *Ber.*, 1892, **25**, 2974.
[4] *Ibid.*, 1912, **45**, 2977.

17. From derivatives of *o*-nitrostyrene, *o*-nitrocinnamic acid, etc.: 

(*a*) In Lipp's indole synthesis [1] an *o*-amino-ω-chlorostyrene is heated with NaOEt at 130–140°:

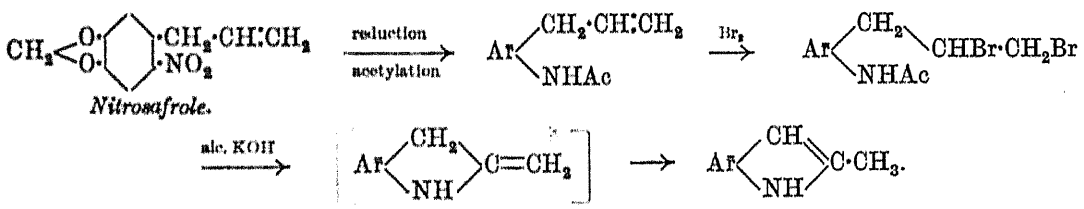


Ruggli [2] has obtained "dindole" by a double application of this method. He finds alcoholic picric acid a convenient reagent for closing the first indole ring. Alcoholic KOH is necessary for the second ring-closure:



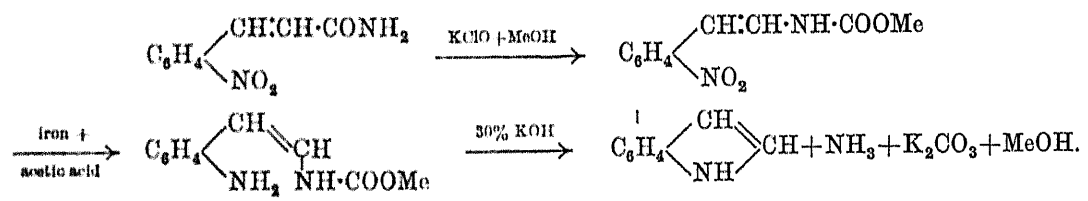
Dindole.

Foulds and Robinson's preparation [3] of 2-methyl-5 : 6-methylenedioxyindole from nitrosafrole is a further example of Lipp's method:



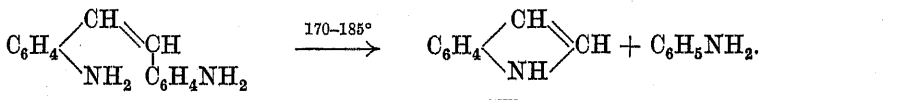
Nitrosafrole.

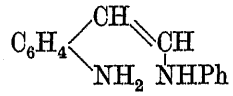
The halogen in these reactions may be replaced by ·NHCOOMe or even by ·C_6H_4·NH_2. Thus Weermann [4] converted *o*-nitrocinnamide into indole by the following series of reactions:



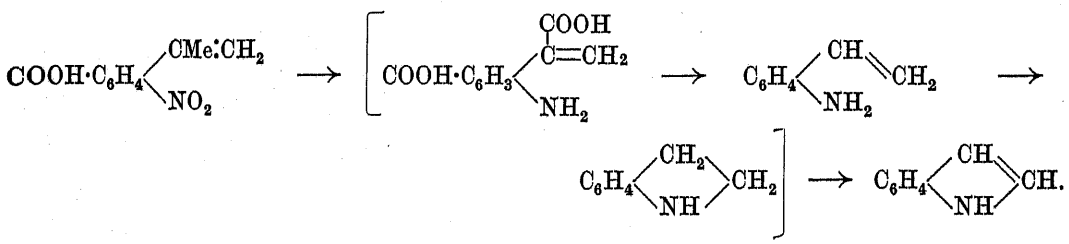
[1] *Ber.*, 1884, **17**, 1067, 2507. [2] *Ibid.*, 1917, **50**, 883. [3] *J. C. S.*, 1914, **105**, 1969.
[4] *Rec. trav. chim.*, 1910, **29**, 18; *Ann.*, 1913, **401**, 14; D.R.-P. 213713.

A quantitative yield of indole is obtained when 2 : 2′-diaminostilbene hydrochloride is heated under reduced pressure at 170–185° : [1]

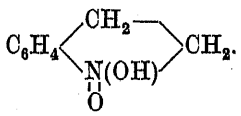


Here it is probable that rearrangement to  precedes the closing of the ring.

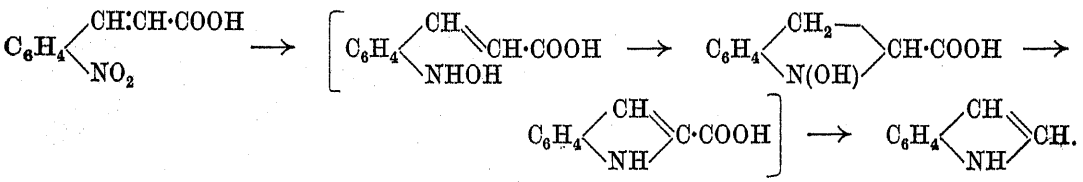
(*b*) A different type of reaction, involving intramolecular addition at the double linkage, is Widman's synthesis of indole by distilling 3-nitro-4-*iso*propenylbenzoic acid with lime.[2] The methyl group is apparently oxidised by the $\cdot NO_2$ and eliminated as CO_2 and H_2O, the NO_2 being itself reduced to $\cdot NH_2$, which then closes the ring by addition at the C : C bond. The yield is very small : *



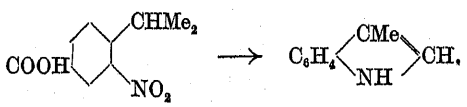
The suggestion of Usherwood and Whitely (see next section) may also apply here, the intermediate being



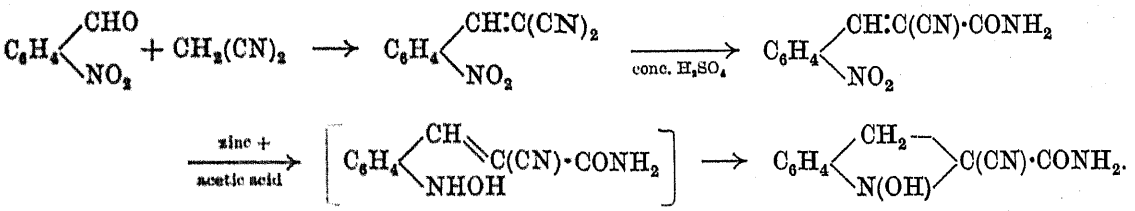
v. Baeyer and Emmerling [3] obtained indole much more satisfactorily by heating *o*-nitrocinnamic acid with iron filings and KOH :



[1] Thiele and Dimroth, *Ber.*, 1895, **28**, 1411; D.R.-P. 84578. [2] *Ber.*, 1872, **15**, 2552.
[3] *Ibid.*, 1869, **2**, 680; Beilstein and Kuhlberg, *Ann.*, 1872, **163**, 141.
* Cf. Fileti, *Gazz.*, 1883, **13**, 350, 378, who reduced *o*-nitrocumic acid with zinc dust and Am_2S and obtained scatole in 10% yield :

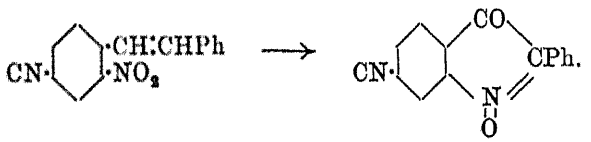


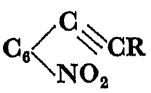
A very similar reaction is described by Heller and Wunderlich : [1]



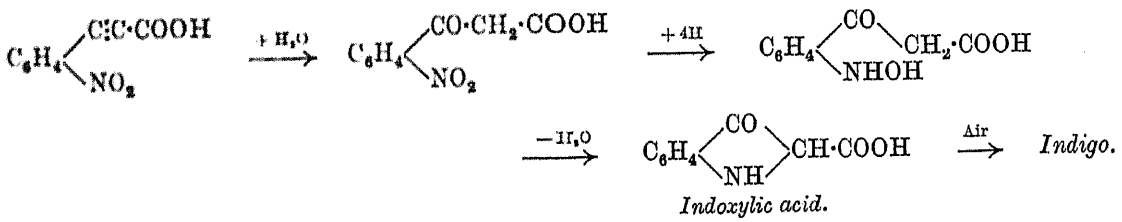
The *N*-hydroxy-compound is converted into 2-cyanodihydroindole-2-carbonamide either by reduction with zinc and ammonia or, curiously enough, by oxidation with chromic acid.

Stoermer and Oehlert [2] assign an indolenone oxide structure to the product of the action of light upon *o*-nitro-*p*-cyanostilbene. The yield is small :



18. From derivatives of *o*-nitrophenylacetylene : 

v. Baeyer in 1880 obtained indigo by the reduction of *o*-nitrophenylpropiolic acid with glucose in alkaline solution.[3] Under these conditions *o*-nitrobenzoylacetic acid is probably an intermediate product :



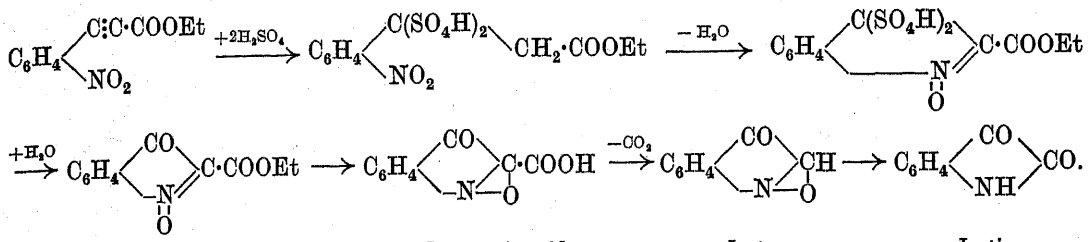
Indoxylic acid.

Indoxylic acid is the final product when ammonium sulphide is used.

o-Nitrophenylpropiolic ester reacts differently with conc. H_2SO_4, isatin being formed in 86% yield.[4] As *o*-nitrobenzoylacetic ester is simply hydrolysed by conc. H_2SO_4, some other

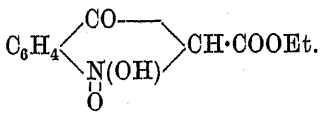
[1] *Ber.*, 1914, **47**, 1617. [2] *Ibid.*, 1902, **55**, 1232.
[3] D.R.-PP. 11857, 11858, 15516.
[4] v. Baeyer, *ibid.*, 1880, **13**, 2259 ; 1881, **14**, 1742 ; D.R.-P. 17656.

intermediate product must be formed from which the isatogenic ester isolated by v. Baeyer is produced. Perkin and Needham [1] suggest the following series of reactions :

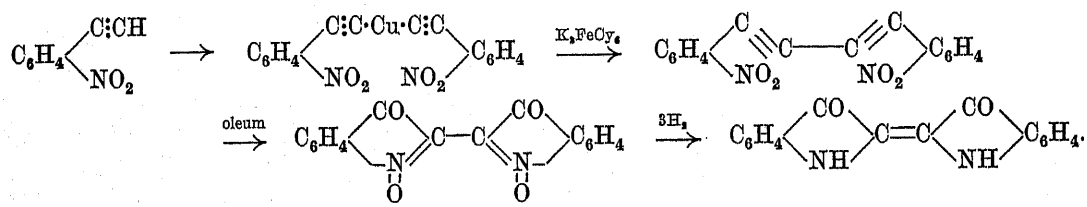


Isatogenic ester (Pfeiffer.) — *Isatogenic acid* (v. Baeyer.) — *Isatogen.* — *Isatin.*

A suggestion has been made by Usherwood and Whiteley [2] that the isatogenic ester (Pfeiffer formula) is derived from an intermediate *aci*nitro-compound :

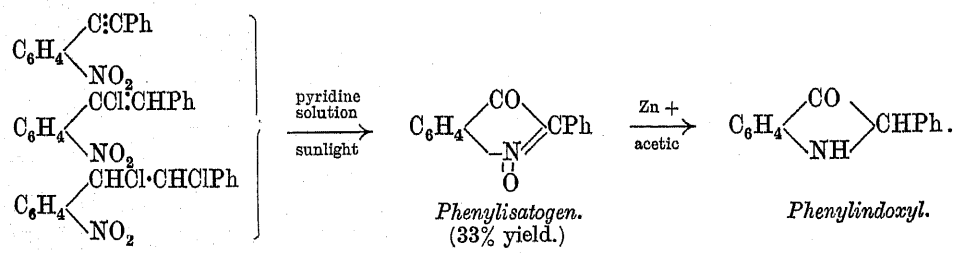


In a similar manner, from dinitrodiphenyldiacetylene v. Baeyer [3] obtained di-isatogen by the action of oleum. This on reduction gave indigo :



Di-isatogen.

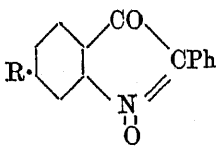
The isatogen reaction has been exhaustively studied by Pfeiffer [4] and by Ruggli.[5] Pfeiffer found that, not only the nitrotolanes, but also the nitrostilbene dichlorides * from which they are prepared are converted in pyridine solution by the action of sunlight into phenylisatogens. Thus :



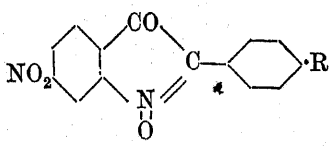
Phenylisatogen. (33% yield.) — *Phenylindoxyl.*

[1] *J. C. S.*, 1904, **85**, 148. [2] *Ibid.*, 1923, **123**, 1077.
[3] *Ber.*, 1882, **15**, 50, 1775; D.R.-P. 19266. [4] *Ber.*, 1912, **45**, 1819; *Ann.*, 1916, **411**, 72–156.
[5] *Ber.*, 1917, **50**, 883; Ruggli and Bolliger, *Helv. Chim. Acta*, 1921, **4**, 626–636.
* See also Stoermer and Oehlert, p. 123.

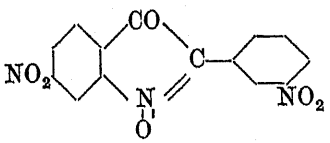
Pfeiffer prepared a series of arylisatogens of the types :

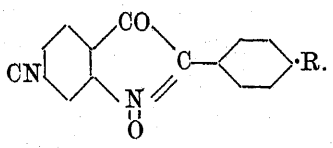


(R = H, ·NO_2, ·CN, ·COOH.)



(R = Me, ·OMe, ·SO_3H, ·OAc, ·OCO·CHMeEt.)

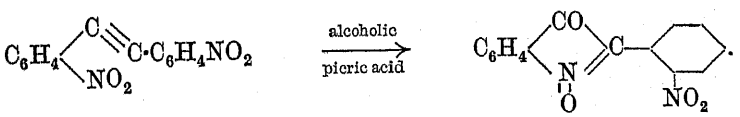




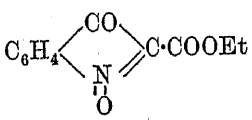
(R = H, Me, ·OMe.)

He also showed that *o*-nitrophenylpropiolic esters gave a 50% yield of the corresponding isatogenic esters when warmed in pyridine. In the case of the 2 : 4-dinitro-derivative, the reaction is so vigorous that the pyridine solution must be cooled.

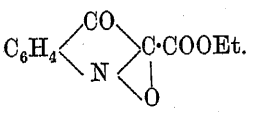
Ruggli [1] used alcoholic picric acid to bring about the conversion of *o* : *o'*-dinitrotolane into *o*-nitrophenylisatogen :



Two forms of isatogenic ester were obtained by Ruggli and Bolliger.[1] By the action of pyridine upon *o*-nitrophenylpropiolic ester Pfeiffer's " quinonoid " isatogenic ester (I) results. This is converted by alcoholic HCl into " *iso*isatogenic ester," to which is assigned the v. Baeyer formula (II). The reverse change is brought about by acetic acid or by heating at 150–160°.



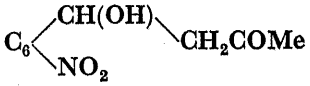
(I.)



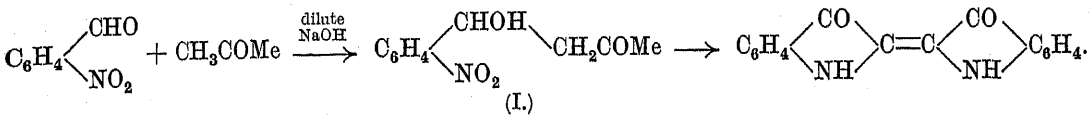
(II.)

Ruggli and Bolliger obtained di-isatogen by the action of sunlight upon *o* : *o'*-dinitrodiphenyldiacetylene.

[1] *Loc. cit.*

19. From *o*-nitrobenzaldehydes and acetone: 

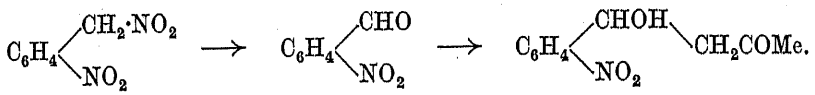
This very general method for the preparation of indigos was discovered by v. Baeyer and Drewson:[1]



(I.)

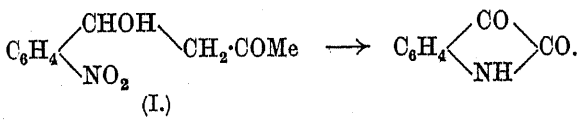
The formation of indigo is rapid and nearly quantitative; indeed the reaction is frequently employed to demonstrate the presence of an *ortho*-nitro group in nitrated aromatic aldehydes.

Pyruvic acid, $CH_3CO{\cdot}COOH$, or acetaldehyde, $CH_3CO{\cdot}H$, may be substituted for acetone.[2] The intermediate "nitrophenyl-lactic methyl ketone" (I) is also obtainable by oxidation of *o*-nitrophenylnitromethane by $KMnO_4$ in the presence of acetone:[3]



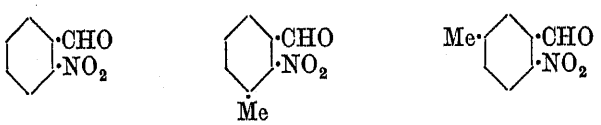
Dichloroacetone gives no indigo but only the *o*-nitrobenzal derivative of the ketone.[4]

By carrying out the condensation in the presence of alkali and an oxidising agent (*e.g.* $KMnO_4$), the intermediate lactic ketone (I) is oxidised to the corresponding isatin. Isatin, 5-methylisatin, 4 : 7- and 5 : 6-dichloroisatins have been prepared in this way:[5]



(I.)

The difficulty of preparing *o*-nitrobenzaldehydes in reasonably good yield has limited the application of v. Baeyer and Drewson's synthesis, and it cannot compete commercially with the glycine methods. The Société des Usines du Rhône did, however, for some time manufacture indigo and dimethylindigos from acetone and the aldehydes



which were prepared from the corresponding nitrotoluene and nitroxylenes by oxidation with MnO_2.[6]

[1] *Ber.*, 1882, **15**, 775, 781, 2856; 1883, **16**, 2205; D.R.-PP. 19768, 20255, 73377, 146294; Koetschet, *Mat. color.*, 1900, **4**, 156.
[2] D.R.-P. 19768. [3] D.R.-P. 238381. [4] Heller, Lauth and Buchwaldt, *Ber.*, 1922, **55**, 483.
[5] D.R.-P. 281052. [6] Koetschet, *loc. cit.*

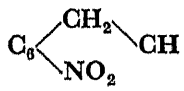
The following *substituted* o-nitrobenzaldehydes have been converted into indigos by the v. Baeyer and Drewson method :

*Nitrobenzaldehyde substituent.**	*References.*	*Nitrobenzaldehyde substituent.*	*References.*
3-Methyl-	6, 11	4-Bromo-	5, 13, 15
5-Methyl-	6, 8, 11	5-Bromo-	1, 3, 4, 10, 15
3-Methoxy-	16	4 : 5-Dichloro-	2, 9
5-Methoxy-	7, 16, 19	3 : 5-Dibromo-	18
4 : 5-Methylenedioxy-	14	3 : 4 : 5-Tribromo-	18
3-Chloro-	15	3 : 5-Dibromo-4-chloro-	18
4-Chloro-	5, 13, 15	3 : 5-Dibromo-4-iodo-	18
5-Chloro-	1, 3, 4, 10, 15	4-Cyano-	17
6-Chloro-	4	5-Acetamino-	12

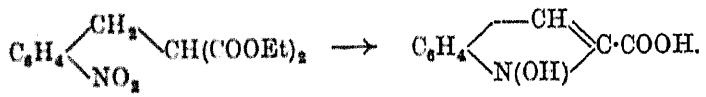
References.

[1] D.R.-P. 30329. [2] D.R.-P. 32238. [3] D.R.-P. 33064. [4] D.R.-P. 112400. [5] D.R.-P. 128727. [6] D. Pat. Anm. S. 11980. [7] D.R.-P. 215785. [8] D.R.-P. 21683. [9] Gnehm, *Ber.*, 1884, **17**, 752. [10] v. Baeyer and Wirth, *Ann.*, 1895, **284**, 154. [11] Koetschet, *Mat. color.*, 1900, **4**, 158. [12] Friedländer and Fritsch, *Monatsh.*, 1903, **24**, 1. [13] Sachs and Kempf, *Ber.*, 1903, **36**, 3301; 1904, **37**, 1862. [14] Hertz, *ibid.*, 1905, **38**, 2853. [15] Schwalbe and Jochheim, *ibid.*, 1908, **41**, 3796. [16] Friedländer, Bruckner and Deutsch, *Ann.*, 1912, **388**, 44, 48. [17] Reich and Lenz, *Helv. Chim. Acta*, 1920, **3**, 150. [18] Janse, *Rec. trav. chim.*, 1921, **40**, 285–317. [19] Halberkann, *Ber.*, 1921, **54**, 3079.

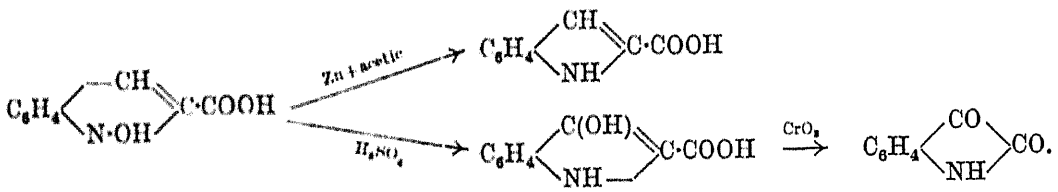
* ·CHO = 1, NO_2 = 2.

20. From o-nitrobenzylmalonic esters, etc. : 

When o-nitrobenzylmalonic ester is boiled with 30% aqueous NaOH intramolecular oxidation occurs and *N*-hydroxyindole-2-carboxylic acid is formed in 80% yield : [1]



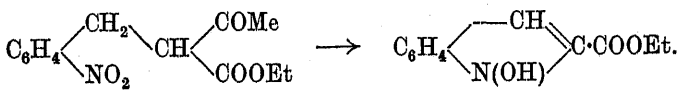
This product may be reduced to indolecarboxylic acid with zinc and acetic acid, or oxidised to isatin with chromic acid. It is isomerised to indoxylic acid by the action of H_2SO_4 :



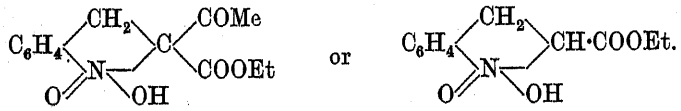
Gabriel, Gerhard and Wolter [2] have extended Reissert's method to o-nitrobenzylacetoacetic

[1] Reissert, *Ber.*, 1896, **29**, 646; D.R.-P. 92794. [2] *Ibid.*, 1923, **56**, 1024.

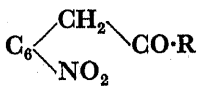
ester. By the action of 3% KOH at 0° this is converted into *N*-hydroxyindole-α-carboxylic acid and the corresponding ester :



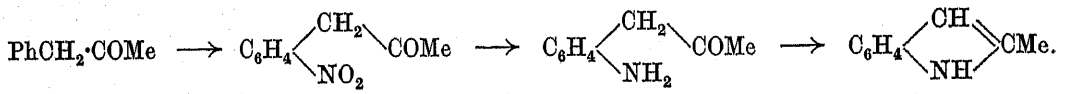
According to Usherwood and Whiteley [1] an *aci*-nitro derivative is formed intermediately in these reactions :



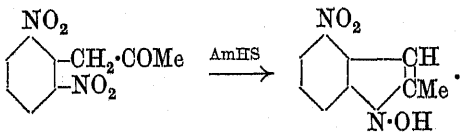
21. From o-nitrobenzyl ketones :



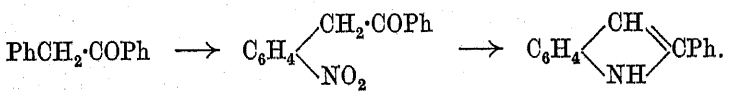
Reduction of *o*-nitrophenylacetone with zinc dust and ammonia gives 2-methylindole in 15% yield [2] :



The 2 : 6-dinitro derivative was reduced with AmSH by Borsche and Rantscheff.[3] One nitro group remains unchanged, the other is reduced to ·NHOH and the product is 1-hydroxy-4-nitro-2-methylindole (75% yield) :



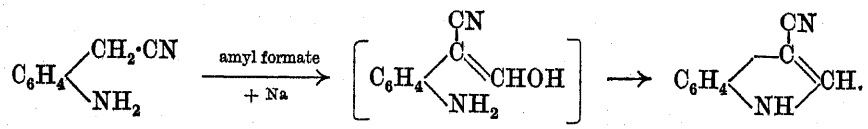
Phenylindole was prepared by Pictet [4] from *o*-nitrodesoxybenzoin [5] :



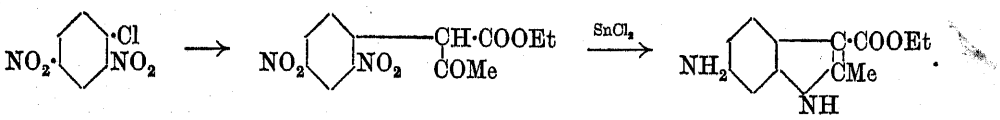
Borsche [6] similarly reduced 2 : 4-dinitrodesoxybenzoin with $SnCl_2$ and obtained 7-amino-2-phenylindole.

[1] *J. C. S.*, 1923, **123**, 1077.
[2] v. Baeyer and Jackson, *Ber.*, 1880, **13**, 187; 1881, **14**, 879.
[3] *Ann.*, 1911, **379**, 178.
[4] *Ber.*, 1886, **19**, 1063.
[5] See also List, *ibid.*, 1893, **26**, 2451.
[6] *Ibid.*, 1909, **42**, 611.

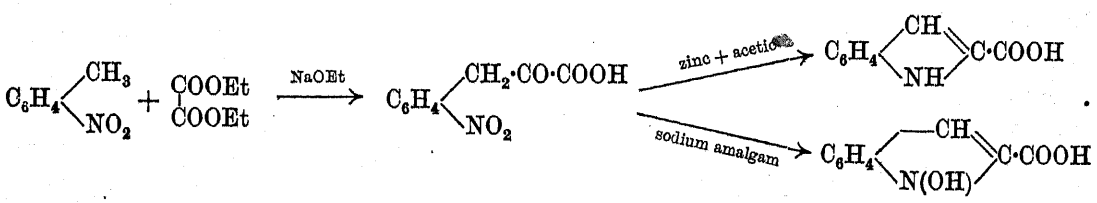
Indole itself results when *o*-nitrophenylacetaldehyde is reduced with iron and acetic acid. Weermann [1] and Pschorr and Hoppe [2] have obtained 3-cyanoindole from the oxymethylene derivative of *o*-aminobenzyl cyanide :



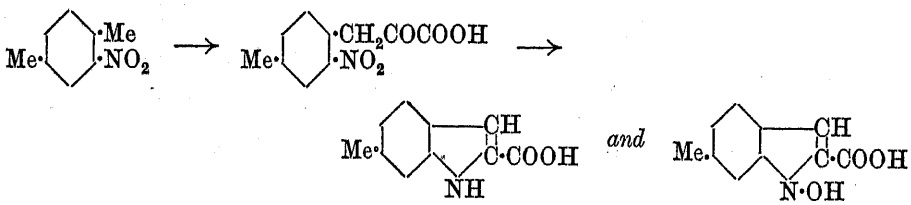
2 : 4-Dinitrophenylacetoacetic ester, reduced with $SnCl_2$, gives a 10% yield of 7-amino-2-methylindole-3-carboxylic ester [3]; *i.e.* the $\cdot COCH_3$ group reacts in preference to the carbethoxy group :



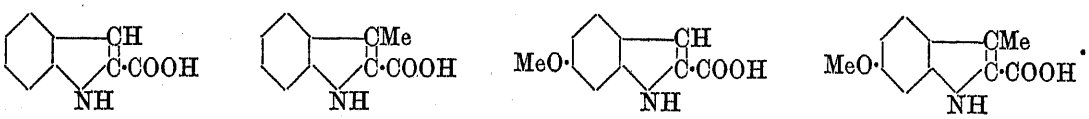
Reissert has also reduced *o*-nitrophenylpyruvic acid, prepared from *o*-nitrotoluene and oxalic ester. With zinc dust and acetic acid the product is indole-2-carboxylic acid, while sodium amalgam gives the *N*-hydroxy compound :



The nitro-*p*-tolylpyruvic acid obtained from nitro-*p*-xylene gives analogous products :

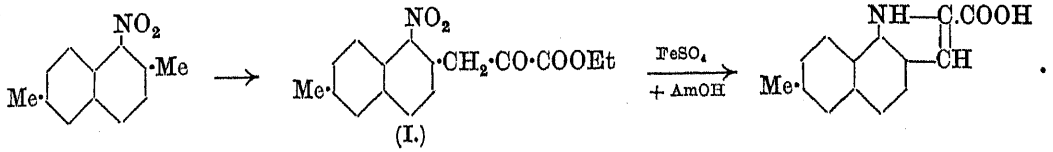


The method has also been used by Kermack, Perkin and Robinson [4] for the preparation of the following indolecarboxylic acids :



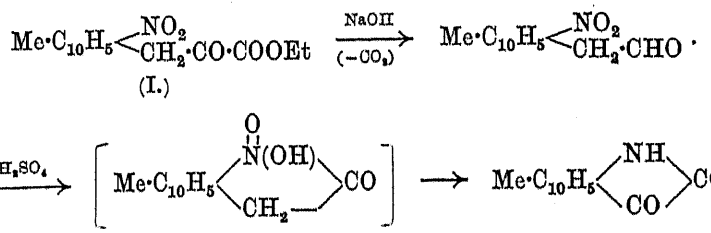
[1] *Rec. trav. chim.*, 1910, **29**, 18.
[2] *Ber.*, 1910, **43**, 2549.
[3] Reissert and Heller, *ibid.*, 1904, **37**, 4369.
[4] *J. C. S.*, 1921, **119**, 1625, 1632, 1634, 1639.

In the naphthalene series Mayer and Alken [1] have obtained 7-methyl-α-naphthindole-2-carboxylic acid from 1-nitro-2 : 6-dimethylnaphthalene :

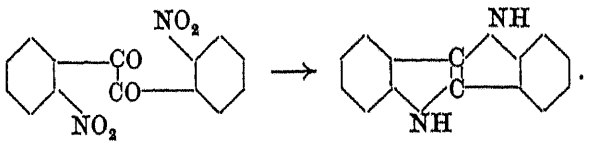


(I.)

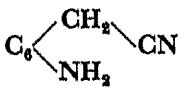
The nitromethylnaphthylpyruvic ester (I) is converted into methyl-α-naphthisatin by successive treatment with NaOH and H_2SO_4 :



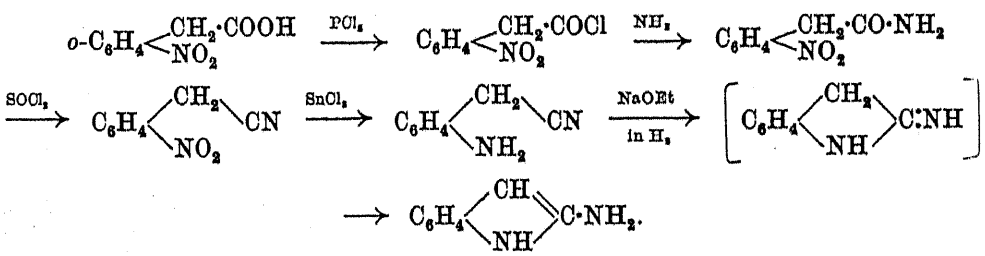
A double application of v. Baeyer and Jackson's method is described by Heller,[2] who reduced 2 : 2′-dinitrobenzil with zinc dust and obtained " dindole " :



Dindole.

22. From *o*-aminobenzyl cyanide : 

2-Aminoindole was prepared by Pschorr and Hoppe [3] by the following method :

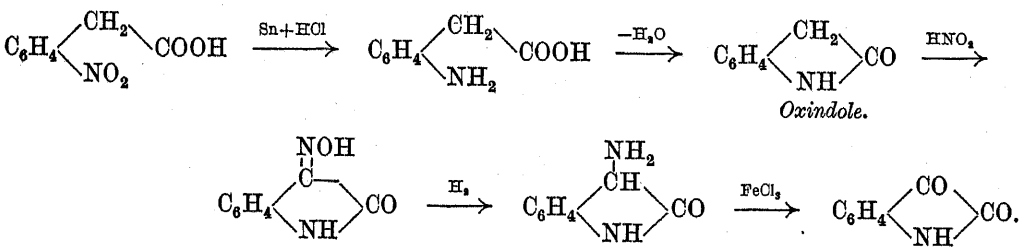


2-Aminoindole.

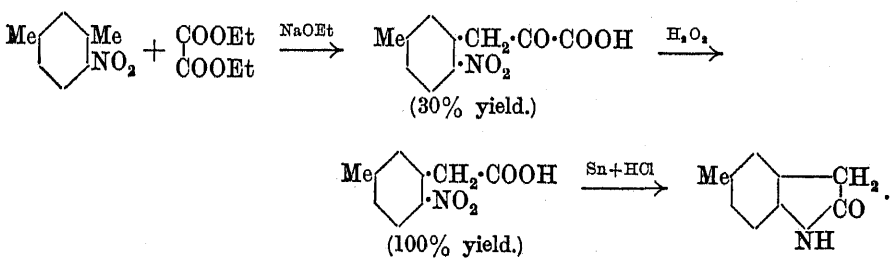
[1] *Ber.*, 1922, **55**, 2283. [2] *Ibid.*, 1917, **50**, 1202. [3] *Ibid.*, 1910, **43**, 584.

23. From *o*-nitrophenylacetic acid, etc.: $C_6H_4(CH_2COOH)(NO_2)$

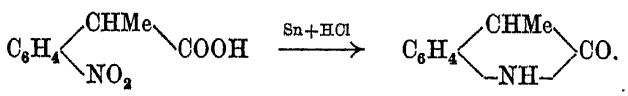
Oxindole was obtained from *o*-nitrophenylacetic acid by v. Baeyer and Knopp in 1878 [1] and led to the first synthesis of isatin: [2]



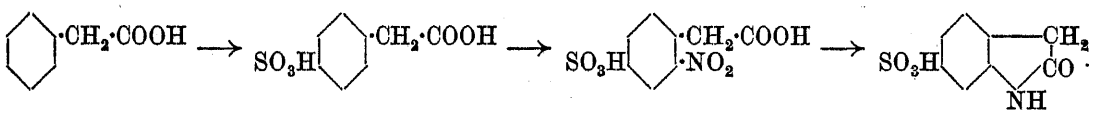
Reissert and Scherk [3] prepared 5-methyloxindole by a similar reaction, starting from 4-nitro-*m*-xylene:



"Atroxindole" (3-methyloxindole) results from the reduction of "*o*-nitrohydratropic acid": [4]



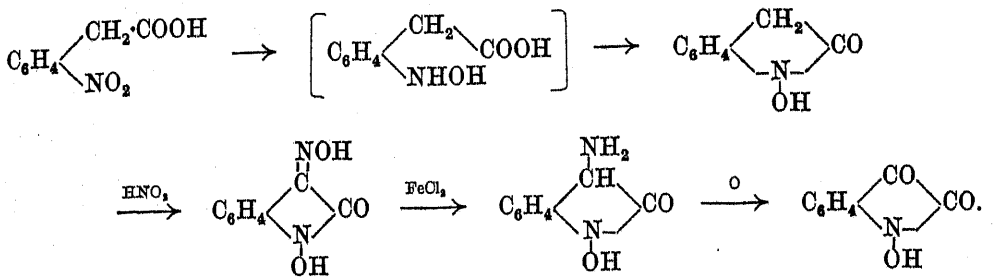
Hausmann [5] sulphonated phenylacetic acid before nitration and so obtained a better yield of *ortho*-nitro compound:



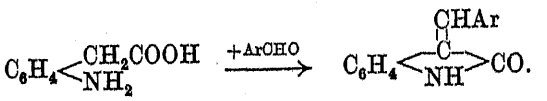
The same method has been used by Martinet and Dornier.[6]

[1] *Ber.*, 1878, **11**, 582. [2] v. Baeyer, *ibid.*, p. 1228. [3] *Ibid.*, 1898, **31**, 387.
[4] Trinius, *Ann.*, 1885, **227**, 274. [5] D.R.-P. 289028. [6] *Compt. rend.*, 1921, **172**, 1415.

The reduction of *o*-nitrophenylacetic acid has been more closely investigated by Reissert,[1] who was able, by using zinc dust and dilute H_2SO_4 at 28–34°, to isolate the *N*-hydroxy compound, from which he prepared by v. Baeyer's method *N*-hydroxyisatin :

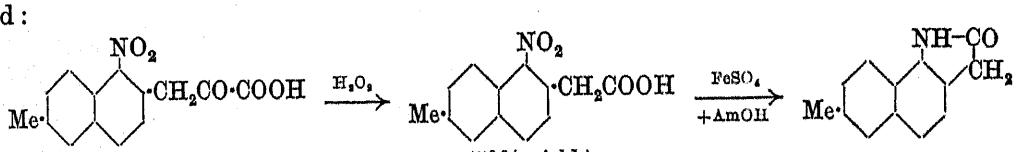


o-Aminophenylacetic acid was first isolated quite recently by Neber.[2] The sodium salt of the nitro-acid was reduced with ferrous sulphate and ammonia and the sodium *o*-aminophenylacetate was treated with the calculated equivalent of HCl. The free acid condenses to oxindole when heated and to benzaloxindoles when boiled with aromatic aldehydes in alcohol solution in the presence of a trace of piperidine : [3]



(Ar = Ph, *o*-, *m*-, *p*-$NO_2 \cdot C_6H_4$·, *o*-, *m*-, *p*-$Cl \cdot C_6H_4$·.)

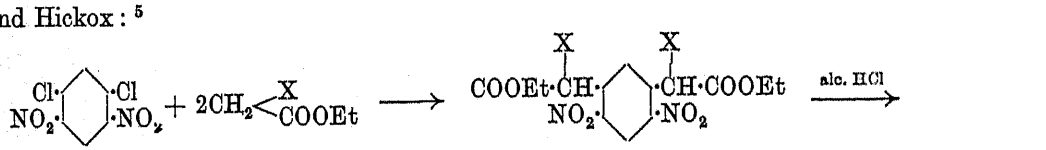
Mayer and Alken [4] have obtained a naphthoxindole from the corresponding naphthylacetic acid :



(See p. 130.)

(50% yield.)

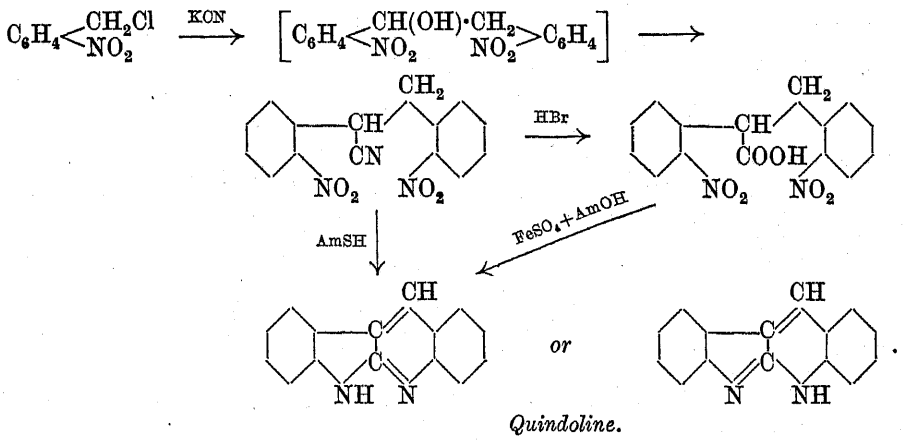
Two double condensations of this type are the preparation of benzo*bis*pyrrolone by Davies and Hickox : [5]



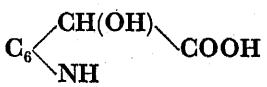
(X = ·COOEt or ·COMe.)

[1] *Ber.*, 1908, **41**, 3921.
[2] *Ibid.*, 1922, **55**, 835.
[3] Neber, *ibid.*, p. 838; Neber and Röcker, *ibid.*, 1923, **56**, 1712; Kliegl and Schmalenbach, *ibid.*, p. 1517.
[4] *Ibid.*, 1922, **55**, 2285.
[5] *J. C. S.*, 1922, **121**, 2640.

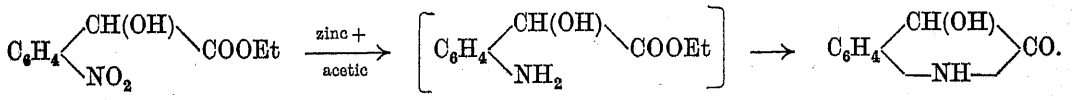
and the synthesis of " quindoline " by Gabriel and Eschenbach : [1]



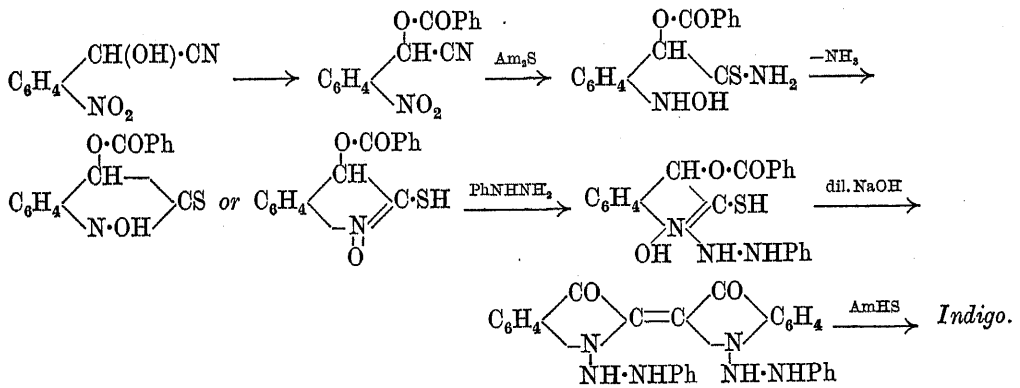
Quindoline.

24. From *o*-nitromandelic acid, etc. (anthroxanic acid) : 

o-Nitromandelic acid was reduced with $SnCl_2$ to dioxindole by Engler and Wöhrle.[2] The ester behaves similarly : [3]

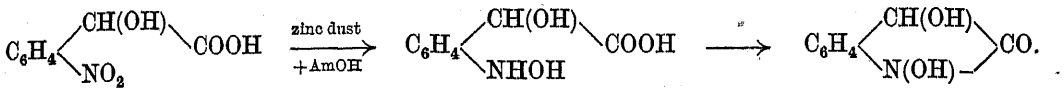


Benzoyldioxindole was prepared by Heller [4] by the action of $SnCl_2$ and HCl upon an alcoholic solution of benzoylated *o*-nitromandelic ester or its amide. The corresponding nitrile was reduced by Albert and Hurtzig [5] with Am_2S :

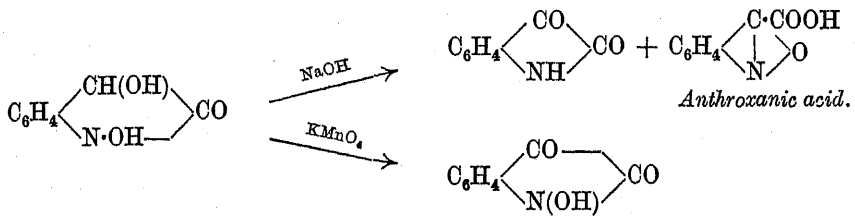


[1] *Ber.*, 1897, **30**, 3019. [2] *Ibid.*, 1887, **20**, 2203. [3] Heller, *ibid.*, 1904, **37**, 949.
[4] *Ibid.*, 1906, **39**, 2338. [5] *Ibid.*, 1919, **52**, 530.

The mild reduction of *o*-nitromandelic acid itself with zinc dust and ammonia yields *N*-hydroxydioxindole : [1]

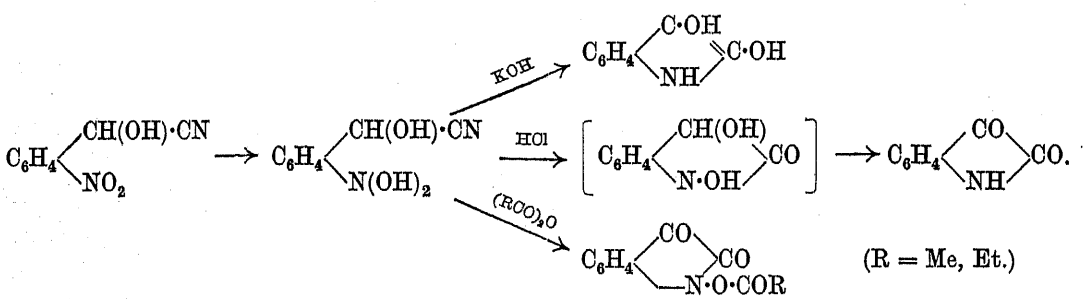


The product is converted by cold NaOH into a mixture of isatin and anthroxanic acid, or it may be oxidised by $KMnO_4$ and acetic acid in acetone to *N*-hydroxyisatin :



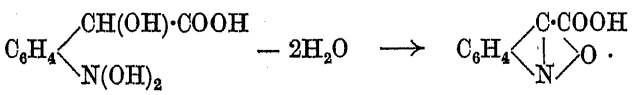
Anthroxanic acid.

The first reduction product of *o*-nitromandelic nitrile, according to Heller [2] is a dihydroxyamine, from which isatin may be obtained by treatment with conc. HCl. KOH converts the dihydroxy body into dioxindole, while acetic and propionic anhydrides give respectively *N*-acetoxy- and *N*-propionoxy-isatin :

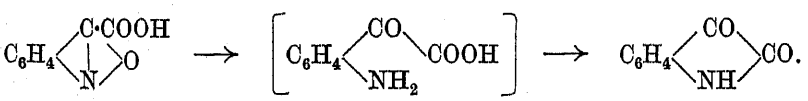


(R = Me, Et.)

The anhydro form of the corresponding dihydroxyaminomandelic acid is anthroxanic acid, which, as has been mentioned, is readily obtainable from *o*-nitromandelic acid :

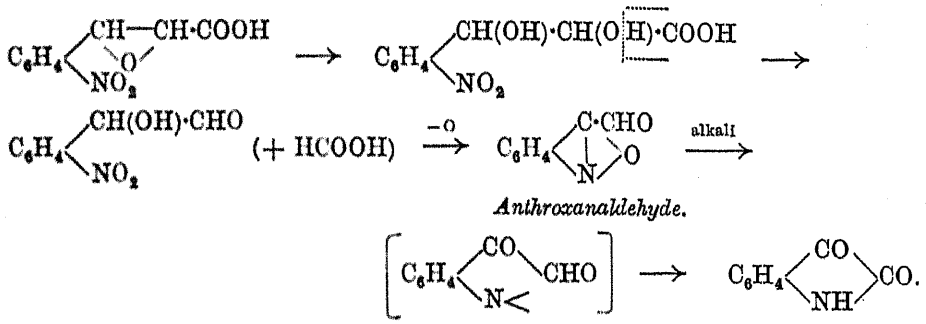


Anthroxanic acid is converted quantitatively into isatin by reduction with ferrous sulphate and ammonia : [3]



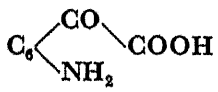
[1] Heller, *Ber.*, 1909, **42**, 473; D.R.-PP. 184693, 184694, 189841, 191855, 195812.
[2] *Ber.*, 1906, **39**, 2339; 1908, **41**, 373.
[3] Schillinger and Wleügel, *ibid.*, 1883, **16**, 2222; Heller, *ibid.*, 1906, **39**, 2344.

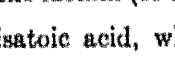
Anthroxanaldehyde, which Schillinger and Wleügel prepared in 10% yield by heating *o*-nitrophenylglycidic acid in acetic acid solution, passes readily into its isomeride, isatin, when treated with aqueous alkali; [1]

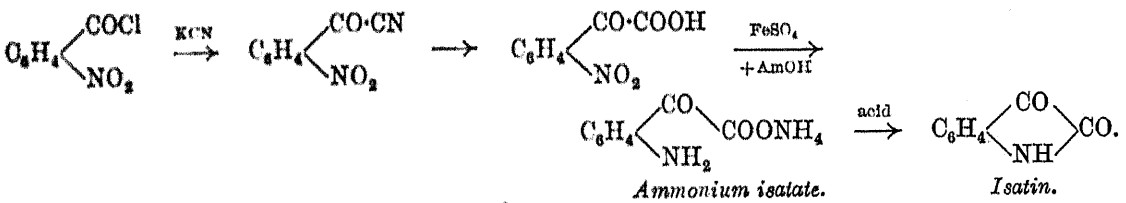


Anthroxanaldehyde.

(Cf. the conversion of methylanthroxan into indoxyl, p. 136.)

25. From *o*-nitrobenzoylformic acid: 

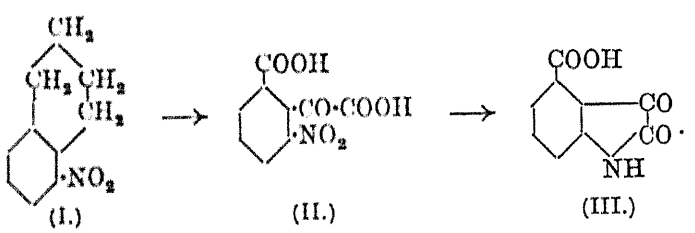
Isatin is the lactam (or lactim) of *o*-aminobenzoylformic acid ("isatic acid"—not to be confused with isatoic acid, which is )—and is formed on acidifying the reduction product of *o*-nitrobenzoylformic acid: [2]



Ammonium isatate. *Isatin.*

The phenylhydrazone of this acid undergoes a similar ring-closure on reduction.[3]

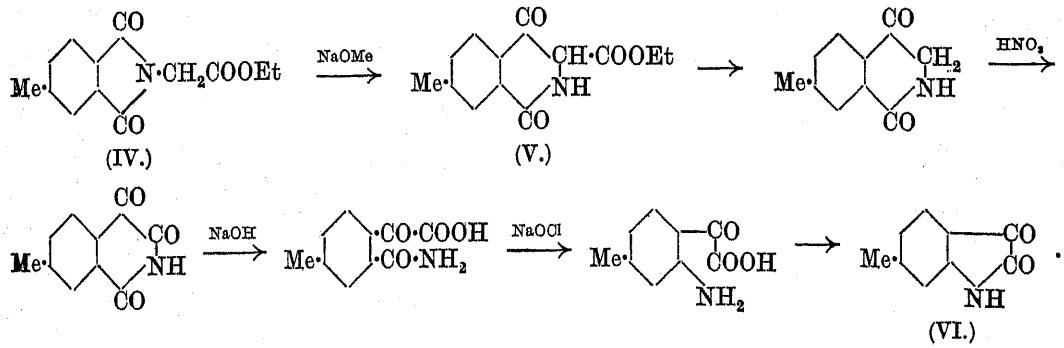
v. Braun and Hahn [4] oxidised nitrotetralin (I) to a nitrocarboxybenzoylformic acid (II), from which they obtained 4-carboxyisatin (III) in 80% yield by reduction with alkali and ferrous sulphate:

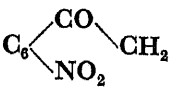


(I.) (II.) (III.)

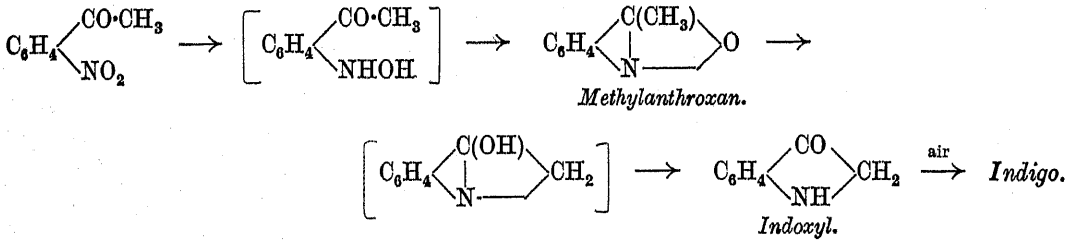
[1] Heller, *Zentr.*, 1910, ii, 975.
[2] Claisen and Shadwell, *Ber.*, 1879, 12, 350.
[3] Krause, *ibid.*, 1890, 23, 3620.
[4] *Ibid.*, 1923, 56, 2344.

A curious series of reactions is recorded by Findeklee,[1] who converted the phthalimide derivative (IV) first into an *iso*quinoline (V) and thence into an isatin (VI) :



26. From *o*-nitroacetophenones or *o*-nitrobenzoylacetic acid : 

The earliest synthesis of indigo was that of Emmerling and Engler,[2] who reduced *o*-nitroacetophenone with zinc dust and soda-lime. Methylanthroxan seems to be formed intermediately, and this gives indoxyl and indigo when heated : [3]



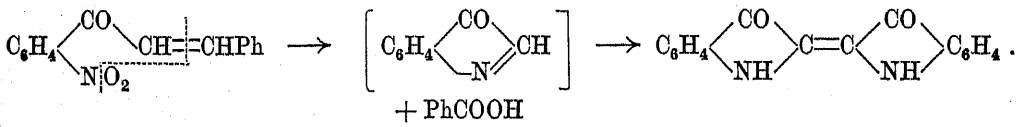
Methylanthroxan.

Indoxyl.

o-Nitro-*p*-tolyl methyl ketone behaves similarly.[4]

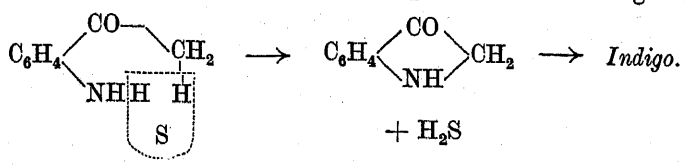
By the reduction of *o*-nitroacetophenone with Sn and HCl, Camps [5] obtained both indigo and hydrazoacetophenone.

Benzal-*o*-nitroacetophenone is quickly converted by the action of light into indigo and benzoic acid : [6]



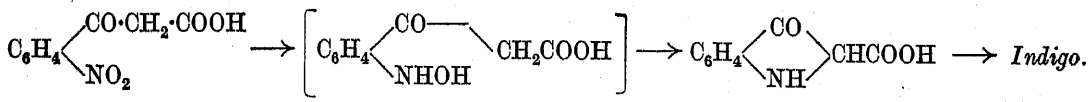
[1] *Ber.*, 1905, **38**, 3551.
[2] *Ibid.*, 1870, **3**, 885; 1895, **28**, 309; see also Wichelhaus, *ibid.*, 1876, **9**, 1106; Gevekhot, *Ann.*, 1883, **221**, 330. [3] Bamberger and Elger, *Ber.*, 1903, **36**, 1624. [4] Duff, *J. C. S.*, 1914, **105**, 2185.
[5] *Ber.*, 1899, **32**, 3232. [6] Engler and Dorant, *ibid.*, 1895, **28**, 2499.

The oxidation of *o*-aminoacetophenone with sulphur at 210–230° gives indigo : [1]



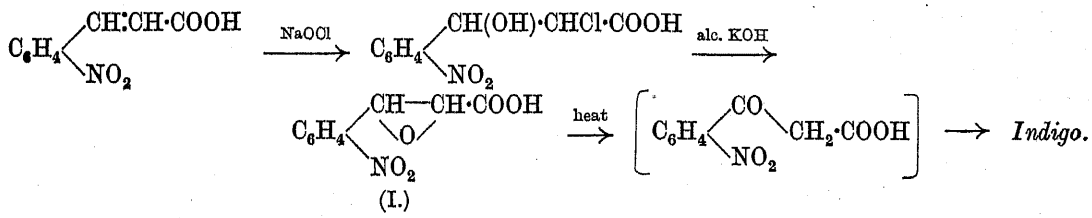
5-Bromo-2-aminoacetophenone and 2-amino-1-naphthyl methyl ketone behave in the same way.

o-Nitrobenzoylacetic acid is not converted into isatogenic acid (see p. 124) by the action of conc. H_2SO_4,[2] but by treatment with dilute KOH and glucose and subsequent air oxidation it gives an almost quantitative yield of indigo : [3]



6 : 6′-Dimethylindigo was similarly prepared by Duff [4] from *o*-nitro-*p*-toluylacetic acid in 50% yield.

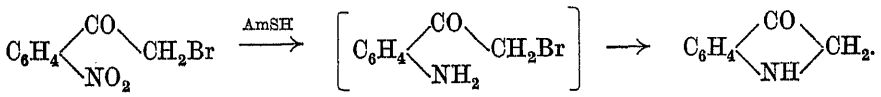
v. Baeyer's synthesis of indigo [5] from the so-called "*o*-nitrophenyloxyacrylic acid" (I) probably proceeds *via* *o*-nitrobenzoylacetic acid :



The yield is only small, for the glycidic acid (I) can also give anthroxanaldehyde under these conditions.

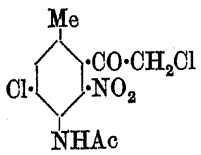
27. From o-aminophenacyl halides, etc. : $C_6\langle^{CO}_{NH_2}\rangle CH_2X$

The reduction of *o*-nitrophenacyl bromide gives indoxyl and thence by air oxidation indigo : [6]

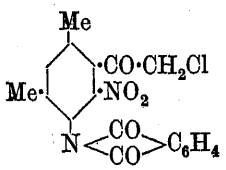


[1] D.R.-P. 273340.
[2] Needham and Perkin, *J. C. S.*, 1904, **85**, 148.
[3] Perkin, *ibid.*, 1914, **105**, 2379, footnote; E.P. 16181/1906; D.R.-P. 201108.
[4] *J. C. S.*, 1914, **105**, 2186.
[5] *Ber.*, 1880, **13**, 2262; D.R.-P. 11857.
[6] Gevekhot, *Ann.*, 1883, **221**, 331; D.R.-P. 23785.

Bodinus [1] has similarly reduced

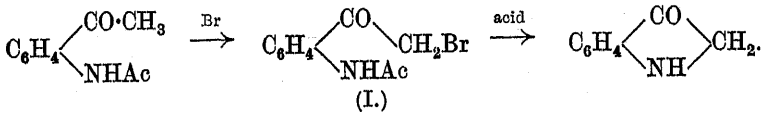


and



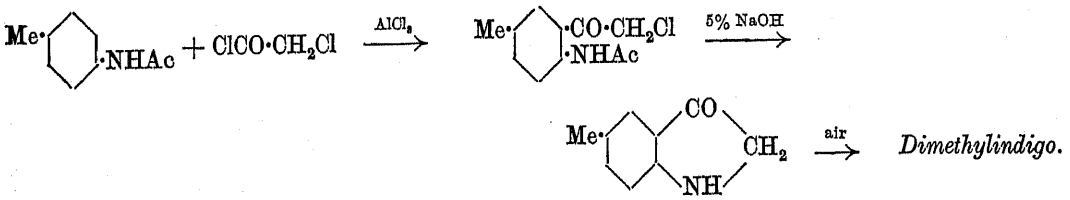
to the corresponding indoxyls.

o-Acetylaminoacetophenone was brominated by v. Baeyer and Bloem [2] and gave indoxyl on subsequent hydrolysis:

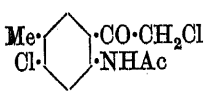


(I.)

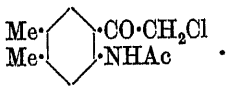
Compounds of the type (I) are more easily prepared by the Friedel-Crafts reaction. From acetyl-*p*-toluidine Kunckell [3] by this method obtained 5 : 5′-dimethylindigo:

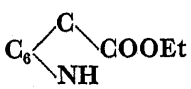


Kunckell and Lillig [4] and Kunckell and Schneider [5] have similarly converted into the corresponding indoxyls and indigos the substances:



and



28. From mesoxalic ester and arylamines: 

Mesoxalic ester, $CO(COOEt)_2$, like its ureide, alloxan, reacts with a number of phenols, amines, etc., much in the same way as formaldehyde. Thus Guyot and Michel [6] found that

[1] *Chem. Zeitung*, 1916, **40**, 326.
[2] *Ber.*, 1884, **17**, 963; D.R.-P. 21592.
[3] *Ibid.*, 1900, **33**, 2648; *Zentr.*, 1912, i, 1214.
[4] *J. pr. Chem.*, 1912, **86**, 517.
[5] *Ibid.*, p. 429.
[6] *Compt. rend.*, 1909, **148**, 229.

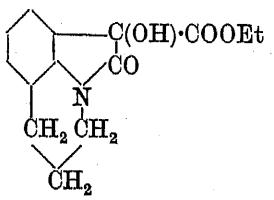
with tertiary amines of the type $PhNR_2$ addition occurred in acetic acid at 100°, with production of the carbinols

$$p\text{-}R_2N\cdot C_6H_4\cdot C(OH)<\begin{matrix}COOEt\\COOEt\end{matrix}.$$

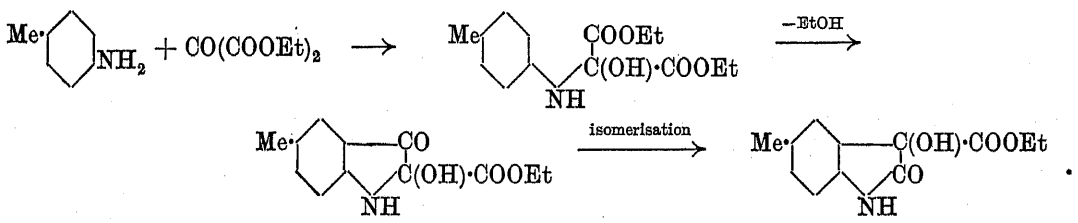
The reaction with primary and secondary aromatic amines was investigated by Guyot and Martinet,[1] who found that here the main product was a dioxindolecarboxylic ester:



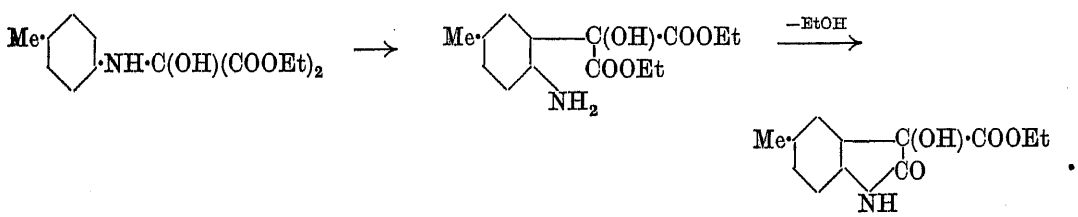
Analogous compounds were obtained from β-naphthylamine, methyl- and ethyl-anilines and ethyl-β-naphthylamine. Tetrahydroquinoline, which may be regarded as an alkylated aniline, behaved quite similarly, the product being



The reaction has been studied further by Martinet,[2] who suggests the following mechanism:



It seems much preferable, however, to suppose that isomerisation takes place *before* ring-closure:



This makes the reaction a special case of that discovered by Guyot and Michel, the *ortho* position being attacked instead of the *para*. Martinet, in fact, found that the yield of dioxindole was greatest with *para* substituted secondary amines.

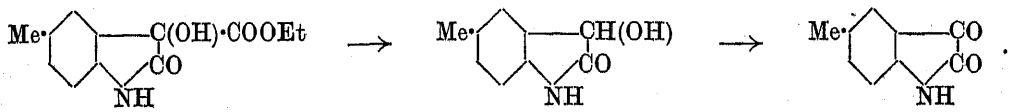
[1] *Compt. rend.*, 1913, **156**, 1625.
[2] *Ibid.*, 1918, **166**, 851, 998; *Ann. Chim.*, 1919, [ix], **11**, 15–84; *Mat. color.*, 1919, **23**, 53–56.

Martinet has obtained isatins from *p*-toluidine, 4-*m*-xylidine, methyl- and ethyl-anilines, methyl- and ethyl-*p*-bromoanilines, α- and β-naphthylamines, ethyl-β-naphthylamine, and the tetrahydro derivatives of quinoline, 6-methylquinoline and 6-methylquinaldine.

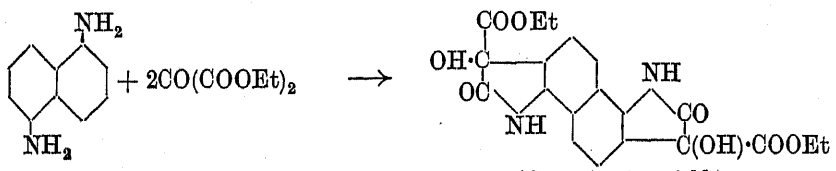
The reaction fails with aniline, *p*-bromoaniline, *p*-aminophenol, *p*-aminodimethylaniline, *m*- and *p*-phenylenediamines, benzidine, carbazole and phenyldihydroacridine.

Halberkann [1] found that, contrary to Martinet's statement, *p*-anisidine reacted normally, giving a 33% yield of the dioxindole derivative. *m*-Toluidine has been converted into a dioxindole by Bonnefoy and Martinet.[2]

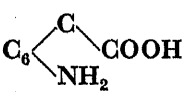
The dioxindole compounds readily lose the carbethoxy group on hydrolysis and in the presence of air give isatins :



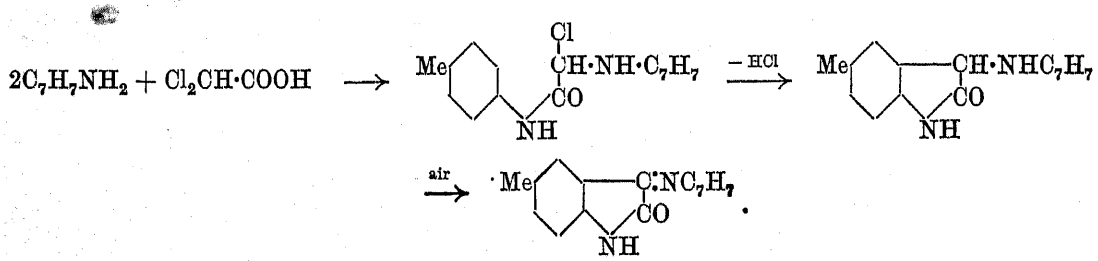
A double application of the reaction is described by Martinet and Vacher : [3]



(Quantitative yield.)

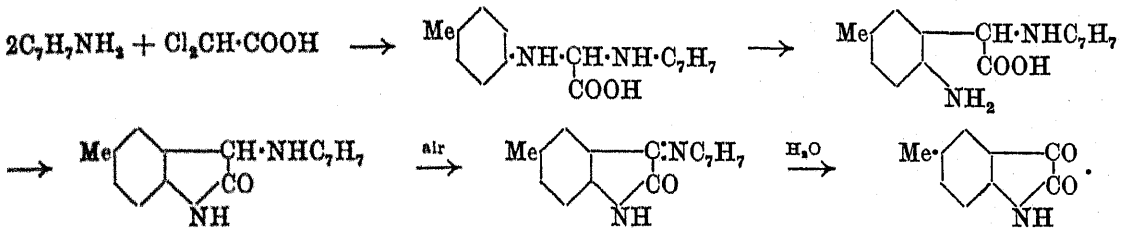
29. From dichloroacetic acid : 

This method is of the same type as Guyot and Martinet's syntheses from mesoxalic ester. P. J. Meyer [4] obtained 5-methylisatin by condensation of *p*-toluidine with dichloroacetic acid. Duisberg [5] considered that ring-closure took place by elimination of HCl from an intermediate toluidide of tolylamino-chloroacetic acid :



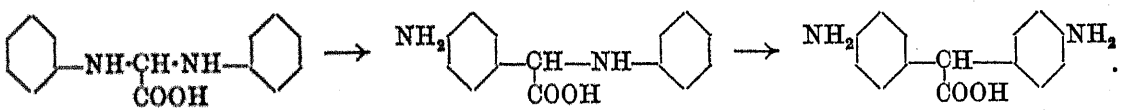
[1] *Ber.*, 1921, **54**, 3080. [2] *Compt. rend.*, 1921, **172**, 220. [3] *Bull.*, 1922, [iv], **31**, 436.
[4] *Ber.*, 1883, **16**, 926, 2261; D.R.-PP. 25136, 27979. [5] *Ber.*, 1885, **18**, 190.

Careful investigations by Heller [1] and Ostromisslensky [2] showed, however, that the changes involved are much less simple. The first product is ditoluidoacetic acid, the ester of which may also be prepared from glyoxylic ester and toluidine acetate. This undergoes a rearrangement similar to the ψ-cumidine change, the acetic acid group moving from the nitrogen to the *ortho* position (the *para* being occupied). Ring-closure then occurs, followed by oxidation to the imesatin and hydrolysis of the toluido group :

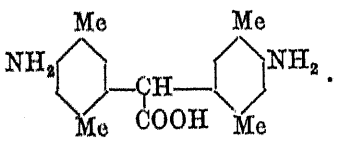


These changes are brought about by adding the ditoluidoacetic acid (or ester), mixed with sand, to oleum at 50°, diluting with conc. H_2SO_4 and finally pouring upon ice. Boiling HCl may also be used.

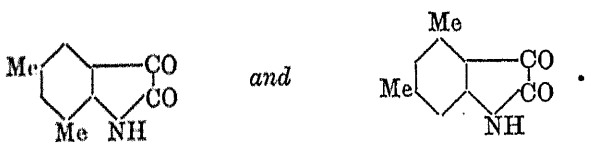
p-Toluidine gives the best yield (60%), but other arylamines have been tried. Aniline forms no isatin,[3] the product being *p* : *p'*-diaminodiphenylacetic acid, the result of two *para* isomerisations :



p-Xylidine behaves like aniline and forms only the compound :



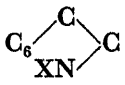
From 4- and 5-*m*-xylidines Heller [4] obtained the corresponding isatins :



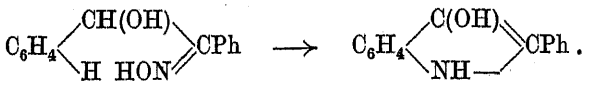
In the second case *para* isomerisation seems to be prevented by the steric effect of the two methyl groups. The yield from 4-*m*-xylidine was about 30%, but Hantzsch and Meyer [5] obtained double this amount by using potassium dichloroacetate in aqueous–alcoholic solution. Ostromisslensky [6] prepared 7-methylisatin from *o*-toluidine (17% yield).

The condensation of glyoxylic acid with toluidine to give 5-methylisatin and its *p*-toluidide is described by Böttinger.[7]

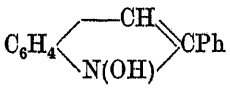
[1] *Ann.*, 1904, **332**, 247; 1908, **358**, 262; *Ber.*, 1908, **41**, 4264.
[2] *Ibid.*, 1907, **40**, 4972; 1908, **41**, 3019, 3029.
[3] Heller, *ibid.*, p. 4264.
[4] *Ann.*, 1908, **358**, 364.
[5] *Ber.*, 1922, **55**, 3189.
[6] *Ibid.*, 1907, **40**, 4973.
[7] *Arch. Pharm.*, 1879, **233**, 100.

30. From benzoin oxime: 

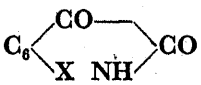
Fischer and Hütz [1] converted benzoin oxime into 2-phenylindoxyl (or 2-phenyl-1-hydroxyindole) by means of conc. H_2SO_4:



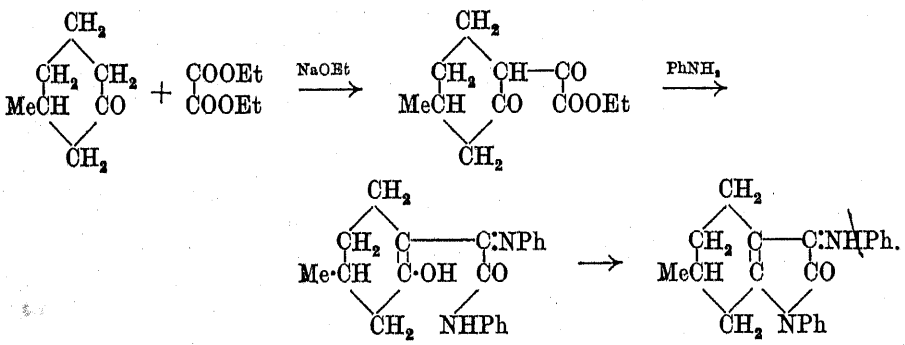
Desoxybenzoin oxime does not undergo this change, nor does the oxime of $PhCH_2 \cdot CHO$. The reaction seems therefore to involve the secondary alcohol grouping in some way. The supposition that the product might be



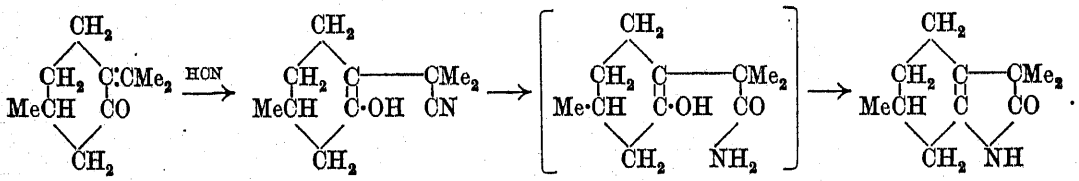
is supported by the formation of *o*-nitrosobenzoic acid on oxidation; but benzoylanthranilic acid is produced at the same time.

31. From cyclic ketones, oxalic ester and amines: 

The condensation product of 3-methyl*cyclo*hexanone and oxalic ester reacts with aniline to give a tetrahydroisatin derivative: [2]



A somewhat similar reaction was described by Lapworth: [3]

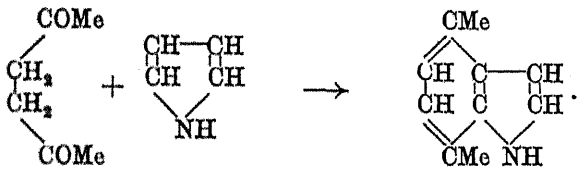


[1] *Ber.*, 1895, **28**, 585; 1896, **29**, 2062.
[2] Kötz and Hesse, *Ann.*, 1905, **342**, 319.
[3] *J. C. S.*, 1906, **89**, 1869.

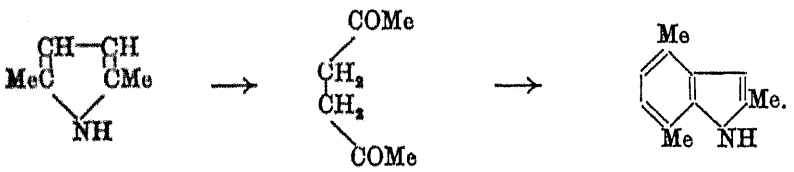
The 1 : 4 additive product is isolated as well as the indole. The former is the only product in the case of other α : β-unsaturated cyclic ketones.

32. From pyrroles or carbazoles

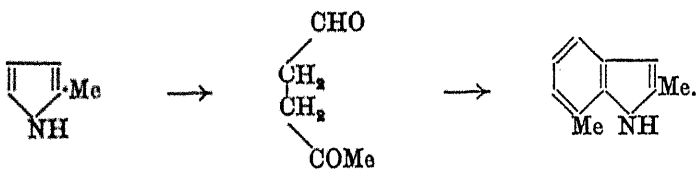
Plancher and his co-workers obtained indoles by the action of zinc acetate and acetic acid at 120° on α-substituted pyrroles. The pyrrole derivative is first hydrolysed to a 1 : 4-diketone or ketoaldehyde, which condenses with a second molecule of the pyrrole. Plancher [1] showed that acetonylacetone condenses with pyrrole itself in the presence of zinc acetate and acetic acid to give 4 : 7-dimethylindole :



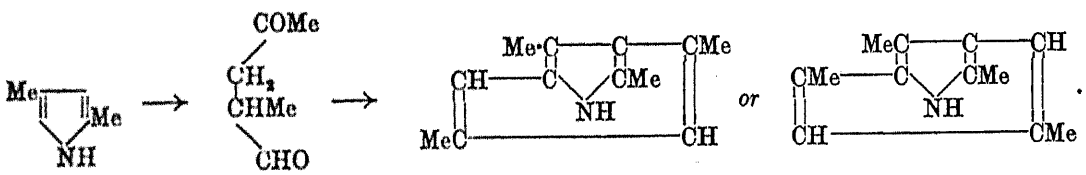
In the case of 2 : 5-dimethylpyrrole an α-methyl group is eliminated : [2]



2-Methylpyrrole gives 2 : 7-dimethylindole : [3]

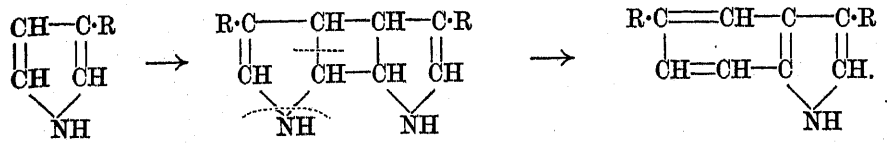


2 : 4-Dimethylpyrrole behaves differently. The α-methyl group is not easily displaced and condensation occurs in the 3 : 5-positions : [4]



[1] *R. A. L.*, 1902, [v], **11**, ii, 210.
[2] Plancher and Tornani, *Gazz.*, 1905, **35**, 461; *Ber.*, 1902, **35**, 606.
[3] Plancher and Ciusa, *R. A. L.*, 1906, [v], **15**, ii, 447.
[4] Plancher and Tornani, *loc. cit.*

The condensed pyrroles obtained by Dennstedt and Zimmermann [1] by treating an ether solution of β-ethyl- or β-*iso*propylpyrrole with HCl gas are converted into indoles by dilute H_2SO_4 : [2]

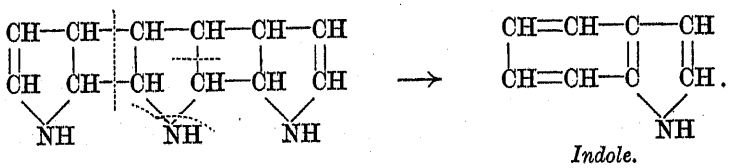


3 : 5-*Dialkylindole* (50% yield.)

(R = Et, ·$CHMe_2$.)

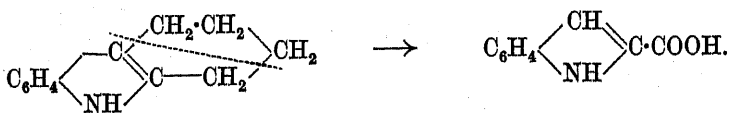
The same product results directly from the action of very dilute H_2SO_4 upon the β-*iso*propylpyrrole.

Tripyrrole, prepared from pyrrole and dry HCl in ether, gives indole when fused with alkali : [3]



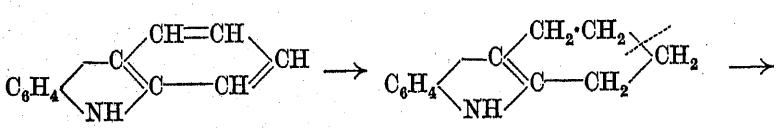
Indole.

Alkaline fusion of tetrahydrocarbazole also yields an indole derivative : [4]

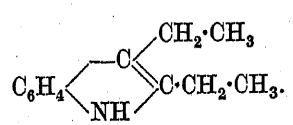


Tetrahydrocarbazole.

The catalytic reduction of carbazole by hydrogen in the presence of heated nickel proceeds differently, diethylindole being formed : [5]

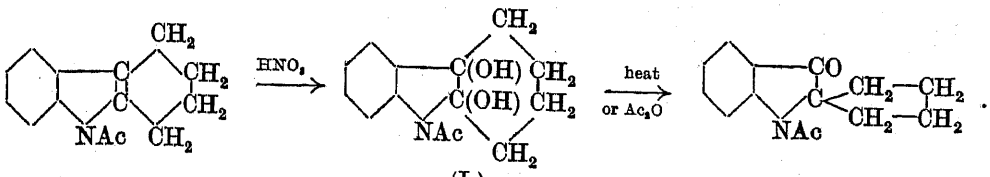


Carbazole. *Tetrahydrocarbazole.*



[1] *Ber.*, 1887, **20**, 856; 1888, **21**, 1478. [2] Dennstedt, *ibid.*, 1888, **21**, 3429. [3] D.R.-P. 125489.
[4] Zanetti, *Ber.*, 1893, **26**, 2006. [5] Padoa and Chiaves, *R. A. L.*, 1908, [v], **16**, ii, 762.

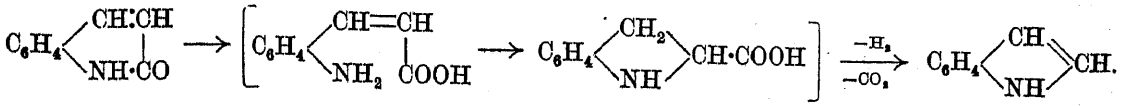
An interesting pinacol-pinacolin change resulting in the conversion of acetyldihydroxyhexahydrocarbazole (I) into an indoxyl derivative (II) is described by Perkin and Plant : [1]



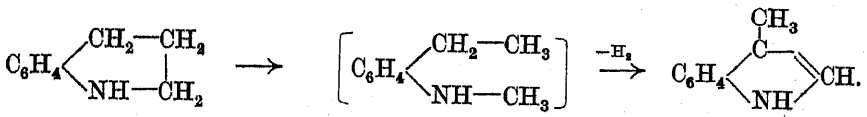
(I.) (II.)

33. From quinolines

One of the earliest syntheses of indole was T. Morgan's alkaline fusion of carbostyril : [2]



Hofmann and Koenigs [3] obtained indole and quinoline in the proportion of 1 : 2 by passing tetrahydroquinoline through a hot tube. A different reaction occurs when tetrahydroquinoline is passed with hydrogen over reduced nickel at 260–280° [4] :



As propylaniline gives no methylindole under these conditions, the ring is probably broken at the 2 : 3 linkage as shown. Quinoline under similar conditions gives 2-methylindole, methyl-*o*-toluidine and *o*-toluidine.

The picrate of 1-methyl-2-propyl-1 : 2-dihydroquinoline (I) gives *N*-propylindole methopicrate (II) when heated in absolute alcohol : [5]

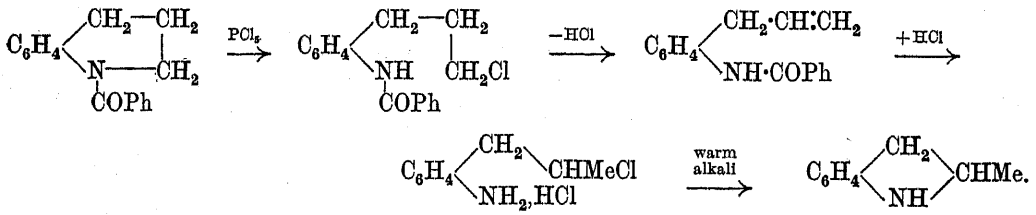


(I.) (II.)

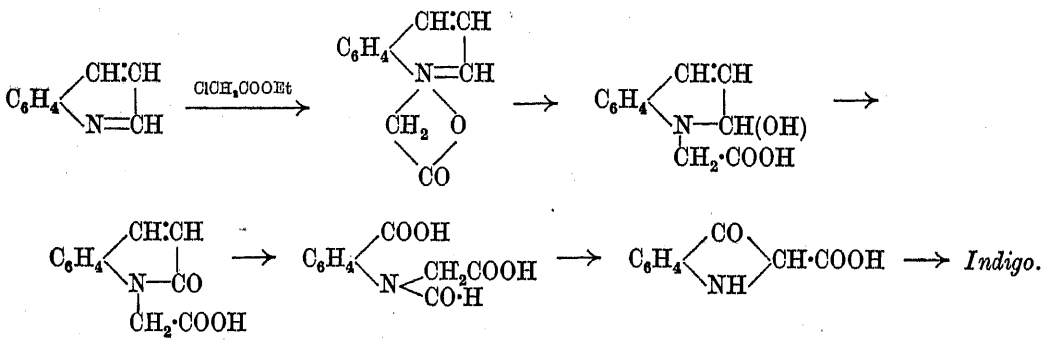
v. Braun and Steindorff [6] have converted tetrahydroquinoline into 2-methyldihydroindole

[1] *J. C. S.*, 1923, **123**, 681. [2] *Chem. News*, 1877, **36**, 269. [3] *Ber.*, 1883, **16**, 738.
[4] Padoa and Carugli, *R. A. L.*, 1906, [v], **15**, i, 113; Padoa and Scagliarini, *ibid.*, 1908, **17**, i, 728.
[5] Meisenheimer and Schütze, *Ber.*, 1923, **56**, 1359. [6] *Ibid.*, 1904, **37**, 4723.

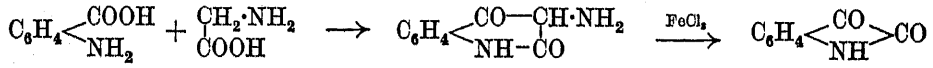
by a series of reactions similar to those by which 2-methylpyrrolidine may be obtained from piperidine (see Pyrroles from Pyridines, p. 87) :



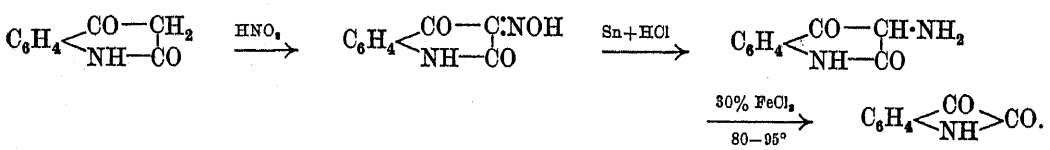
Quinoline forms an additive product with chloroacetic ester, which can be converted into indigo by oxidation with $KMnO_4$, the alkaline filtrate being evaporated and heated at 200°. In all probability formylphenylglycine-*o*-carboxylic acid is an intermediate product : [1]



According to a German Patent [2] isatin is obtained by heating with $FeCl_3$ the dihydroxy-3-aminoquinoline hydrochloride prepared from anthranilic acid and glycine : [3]



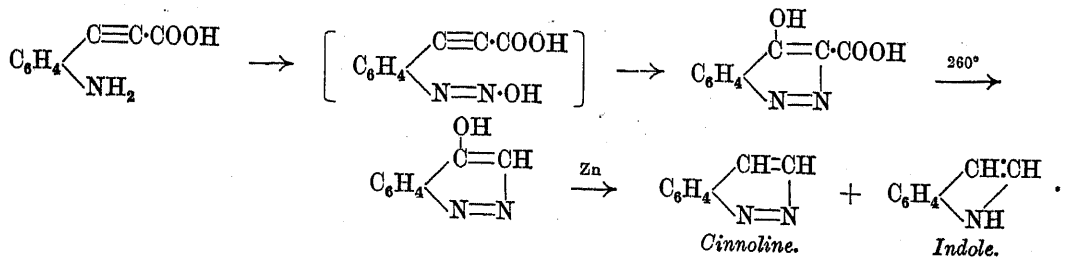
or from 2 : 4-dihydroxyquinoline :



[1] Decker and Kopp, *Ber.*, 1906, **39**, 72. [2] D.R.-P. 292394. [3] D.R.-PP. 102894, 117167.

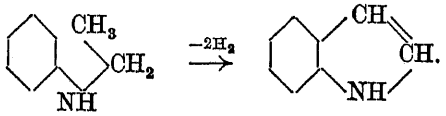
34. From 4-hydroxycinnoline: $C_6<\begin{smallmatrix}C\\N_2\end{smallmatrix}>C$

Diazotisation of *o*-aminophenylpropiolic acid gives, by internal condensation, 4-hydroxycinnoline-3-carboxylic acid, which at 260° loses CO_2 and forms 4-hydroxycinnoline. When this compound is distilled with zinc dust there is obtained, in addition to cinnoline, a certain amount of indole: [1]



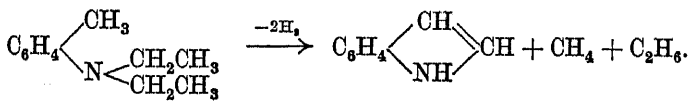
35. Pyrogenous syntheses

Just as diethylamine passed through a hot tube gives pyrrole, so ethylaniline forms traces of indole: [2]



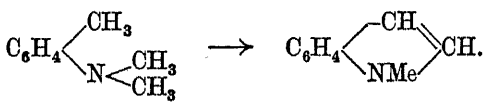
Diethylaniline, methylethylaniline and ethylacetanilide give rather more indole.

Dimethyl-*o*-toluidine yields a little indole, but the best results (3–5%) are obtained with diethyl-*o*-toluidine.



Diethyl-*p*-toluidine gives no methylindole.

The Sabatier-Senderens method is more fruitful. Carrasco and Padoa [3] obtained 1-methylindole in 24% yield from dimethyl-*o*-toluidine passed with hydrogen over reduced nickel at 300–330°:

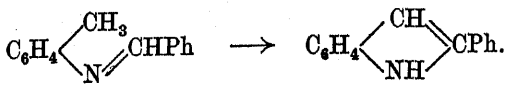


Methyl-*o*-toluidine similarly gave an 8% yield of indole itself.[4]

[1] Richter, *Ber.*, 1883, **16**, 679.
[2] v. Baeyer and Caro, *ibid.*, 1877, **10**, 692, 1263.
[3] *R. A. L.*, 1906, [v], **15**, ii, 729.
[4] *Ibid.*, p. 699.

Fileti [1] obtained indole by distilling cumidine over hot PbO.

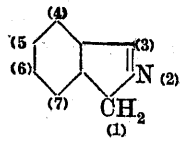
Étard's "methylphenanthridine," [2] obtained by passing benzal-*o*-toluidine through a hot tube, was shown by Pictet [3] to be 2-phenylindole:



[For pyrogenous syntheses from tetrahydroquinolines, see "Indoles from Quinolines," p. 145.]

[1] *Ber.*, 1884, **16**, 2928.
[2] *Compt. rend.*, 1882, **95**, 730.
[3] *Ber.*, 1886, **19**, 1063; Pictet and Erlich, *Ann.*, 1891, **266**, 153.

CHAPTER V

*iso*INDOLES, 

Introductory :

ALL the synthetic methods for *iso*indoles are essentially of one type, the nitrogen atom being applied in the form of ammonia or amines to an aromatic compound containing two suitably reactive *ortho* carbon groups :

$$C_6H_4\!<\!\begin{matrix}CX\\CX\end{matrix} + NH_2R \longrightarrow C_6H_4\!<\!\begin{matrix}C\\C\end{matrix}\!>\!NR.$$

o-Xylylene dibromide gives *N*-substituted *dihydroisoindoles* when treated with primary amines (sect. 2). *Dihydroisoindole* itself can only be obtained indirectly from *o*-xylylene dibromide (sect. 2), but may be prepared by heating xylylenediamine hydrochloride (sect. 1). A similar elimination of ammonia occurs when *o*-cyanobenzylamines are hydrolysed with alkali (sect. 3).

The replacement of the ethereal oxygen by ·NR· in phthalide derivatives (sect. 4) and phthalic anhydrides (sect. 5),

$$C_6H_4\!<\!\begin{matrix}CR_2\\CO\end{matrix}\!>\!O \quad \textit{and} \quad C_6H_4\!<\!\begin{matrix}CO\\CO\end{matrix}\!>\!O,$$

leads to *phthalimidines* and *phthalimides*.

Phthalimides are, of course, the most important class of *iso*indole derivatives, and the various methods by which they may be prepared are grouped in section 5.

The reduction of phthalazines (I) to iso*indoles* (sect. 6) takes place so readily as to suggest that the former are really *N*-amino*iso*indoles (II) :

$$C_6\!<\!\begin{matrix}C\text{——}N\\C\text{——}NR\end{matrix}$$
(I.)

$$C_6\!<\!\begin{matrix}C\\C\end{matrix}\!>\!N\cdot NR.$$
(II.)

1. From *o*-xylylenediamine : $C_6H_4\!<\!\begin{matrix}C\text{—}NH_2\\C\cdot X\end{matrix}$

When the hydrochloride of *o*-xylylenediamine is rapidly heated ring-closure occurs, giving dihydro*iso*indole : [1]

$$C_6H_4\!<\!\begin{matrix}CH_2\text{——}NH_2,HCl\\CH_2\cdot NH_2,HCl\end{matrix} \longrightarrow C_6H_4\!<\!\begin{matrix}CH_2\\CH_2\end{matrix}\!>\!NH.$$

[1] Gabriel and Pinkus, *Ber.*, 1893, **26**, 2213.

2. From *o*-xylylene dibromide: $C_6{<}{CX \atop CX} + NH_2R$

By the action of ammonia upon *o*-xylylene dibromide there is formed a *spiro*cyclic quaternary ammonium bromide: [1]

$$2C_6H_4{<}{CH_2Br \atop CH_2Br} \xrightarrow{NH_3} C_6H_4{<}{CH_2 \atop CH_2}{>}\underset{\displaystyle Br}{N}{<}{CH_2 \atop CH_2}{>}C_6H_4.$$

The simple dihydro*iso*indole, unobtainable by this method, was prepared by v. Braun [2] by the following indirect methods:

(*a*) $$C_6H_4{<}{CH_2Br \atop CH_2Br} + RNH_2 \longrightarrow C_6H_4{<}{CH_2 \atop CH_2}{>}NR \xrightarrow{CNBr}$$

$$C_6H_4{<}{CH_2 \atop CH_2}{>}N{<}\begin{matrix}R\\CN\\Br\end{matrix} \xrightarrow{heat} C_6H_4{<}{CH_2 \atop CH_2}{>}N{\cdot}CN + RBr \xrightarrow{NaOH} C_6H_4{<}{CH_2 \atop CH_2}{>}NH + CO_2 + NH_3.$$

(R = benzyl or allyl; if R = methyl or ethyl the fission with cyanogen bromide regenerates methyl- or ethyl-*iso*indole.)

(*b*) $$C_6H_4{<}{CH_2Br \atop CH_2Br} + NaNHCN \longrightarrow C_6H_4{<}{CH_2 \atop CH_2}{>}N{\cdot}CN \xrightarrow{NaOH} C_6H_4{<}{CH_2 \atop CH_2}{>}NH.$$

(*c*) $$C_6H_4{<}{CH_2 \atop CH_2}{>}\underset{\displaystyle Br}{N}{<}{CH_2 \atop CH_2}{>}C_6H_4 \xrightarrow{NH_3} C_6H_4{<}{CH_2{\cdot}NH{\cdot}CH_2 \atop CH_2{\cdot}NH{\cdot}CH_2}{>}C_6H_4 \xrightarrow[\text{with water}]{\text{warmed}} 2C_6H_4{<}{CH_2 \atop CH_2}{>}NH.$$

The *spiro*-derivative gives dihydro*iso*indole and the ten-membered ring-compound in about equal amounts (22–25%) when heated at 250° with excess of aqueous ammonia.

The *spiro*-piperidinium bromide (I) may be used in a similar manner, the yield of dihydro-*iso*indole being 30%.

$$C_6H_4{<}{CH_2 \atop CH_2}{>}\underset{\displaystyle Br}{N}{<}{CH_2{\cdot}CH_2 \atop CH_2{\cdot}CH_2}{>}CH_2 \qquad \text{(I.)}$$

The action of primary and secondary amines upon *o*-xylylene dibromide has been studied by Scholtz and others. With primary amines the product is a dihydro*iso*indole except when the amine contains an *ortho*substituent. Thus aniline gives *N*-phenyl*iso*indole (II), but with *o*-toluidine only the diamine (III) is obtained.

$$C_6H_4{<}{CH_2 \atop CH_2}{>}NPh \qquad\qquad C_6H_4{<}{CH_2{\cdot}NH{\cdot}C_7H_7 \atop CH_2{\cdot}NH{\cdot}C_7H_7}.$$

(II.) (III.)

[1] Scholtz, *Ber.*, 1891, **24**, 2402; v. Braun and Nelken, *ibid.*, 1922, **55**, 2061.
[2] *Ibid.*, 1910, **43**, 1353; 1913, **46**, 1790; 1922, **55**, 2062.

Secondary amines react to form quaternary ammonium salts :

$$C_6H_4<\begin{matrix}CH_2Br\\CH_2Br\end{matrix} + NHR_2 \longrightarrow C_6H_4<\begin{matrix}CH_2\\CH_2\end{matrix}>\underset{\displaystyle Br}{\overset{\displaystyle |}{N}}R_2.$$

The action of ammonia is simply a special case of this type, the dihydro*iso*indole first formed being attacked by unreacted dibromide :

$$C_6H_4<\begin{matrix}CH_2Br\\CH_2Br\end{matrix} + NH<\begin{matrix}CH_2\\CH_2\end{matrix}>C_6H_4 \longrightarrow C_6H_4<\begin{matrix}CH_2\\CH_2\end{matrix}>\underset{\displaystyle Br}{\overset{\displaystyle |}{N}}<\begin{matrix}CH_2\\CH_2\end{matrix}>C_6H_4.$$

Methylaniline and diphenylamine fail to bring about ring-closure, the products being diamines (IV).

$$C_6H_4<\begin{matrix}CH_2\cdot NR_2\\CH_2\cdot NR_2\end{matrix}$$
(IV.)

$$C_6H_4<\begin{matrix}CH_2\cdot NR_3Br\\CH_2\cdot NR_3Br\end{matrix}.$$
(V.)

Tertiary aliphatic amines form *bis*-quaternary ammonium bromides (V), while tertiary aromatic amines do not react with *o*-xylylene dibromide.

The reaction has been successful with the following amines :

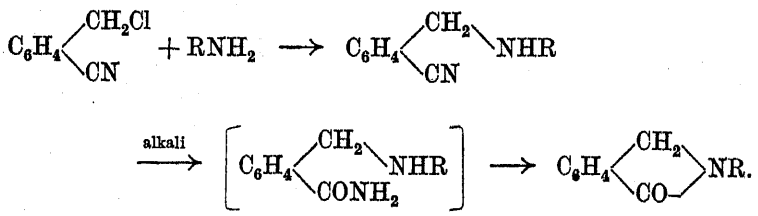
(*a*) *Primary amines.*	*References.*	(*b*) *Secondary amines.*	*References.*
Cyanamide.	7	Diethylamine.	2, 3
Methylamine.	7	Dipropylamine.	6
Ethylamine.	7	Di*iso*butylamine.	2
tert.-Butylamine.	6	Di*iso*amylamine.	6
Allyl.	7	Dibenzylamine.	6
Benzylamine.	2, 7	Piperidine.	2, 3, 9
o-Methylbenzylamine.	5	Tetrahydroquinoline.	6
Aniline.	1, 2, 3, 4	2-Methyldihydroindole.	8
m- and *p*-Chloroanilines.	4		
m- and *p*-Toluidines.	2		
p-Anisidine.	2		
p-Phenetidine.	3		
m-Aminobenzoic acid.	4		
p-Aminoacetophenone.	6		
β-Naphthylamine.	5		

References.

[1] Leser, *Ber.*, 1883, **17**, 1825. [2] Scholtz, *ibid.*, 1898, **31**, 421. [3] Partheil and Schumacher, *ibid.*, p. 591. [4] Scholtz, *ibid.*, p. 628. [5] *Idem*, *ibid.*, p. 1158. [6] Scholtz and Wolfrum, *ibid.*, 1910, **43**, 2310. [7] v. Braun, *ibid.*, p. 1353; 1913, **46**, 1790. [8] Scholtz, *ibid.*, 1914, **47**, 2165. [9] v. Braun and Nelken, *ibid.*, 1922, **55**, 2060.

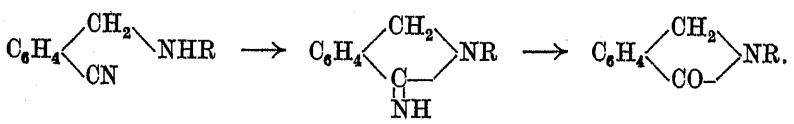
3. From *o*-cyanobenzylamines: $C_6<^{CH_2}_{CONH_2}>NHR$

The hydrolysis of *o*-cyanobenzylamines by aqueous KOH or K_2CO_3 yields phthalimidines: [1]



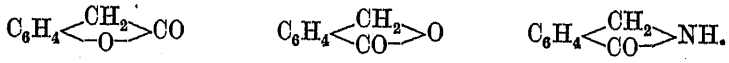
(R = methyl, *iso*butyl, phenyl.)

It is possible that the *iso*indole ring is closed before hydrolysis:



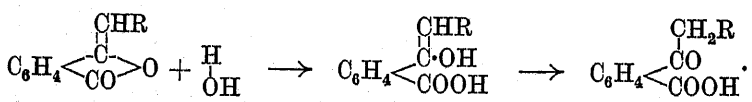
4. From derivatives of phthalide: $C_6<^{C}_{CO}>O + NH_2R$

Although coumaranone (I) cannot be converted directly into oxindole, phthalide (II), in which both the oxygen linkages are aliphatic, readily yields phthalimidine (III) by the action of ammonia:



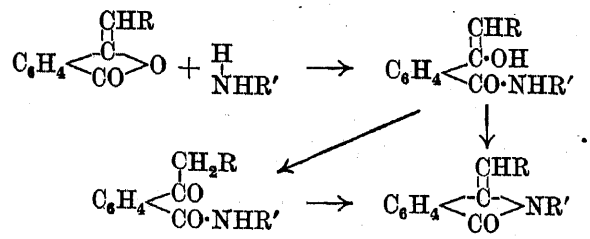
(I.) (II.) (III.)

Alkylidene- and arylidene-phthalides (which are readily obtained by Perkin's reaction from phthalic anhydride and alkyl- or aryl-acetic acids) give on hydrolysis *o*-carboxyketones:



[1] O. Fischer and Wolter, *J. pr. Chem.*, 1909, **80**, 102.

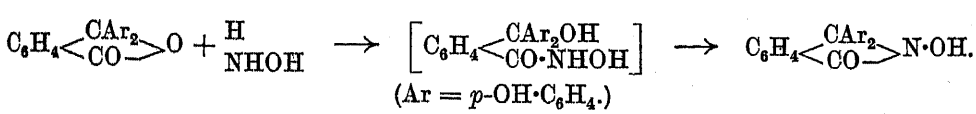
With ammonia or primary amines an amide-ketone is formed, which is quickly converted into a phthalimidine derivative :



The cases investigated are the following :

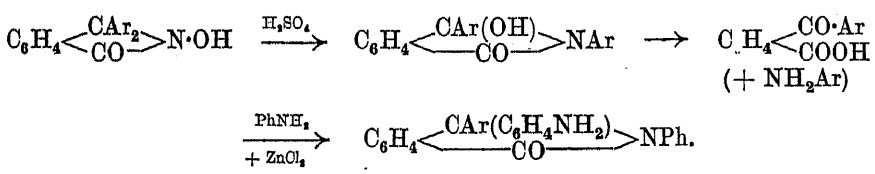
R.	*R'.*	*References.*
Ph	H, Et	Gabriel, *Ber.*, 1885, **18**, 2434.
o-C_7H_7	H	Bethmann, *ibid.*, 1899, **32**, 1104.
m-C_7H_7	H	Heilmann, *ibid.*, 1890, **23**, 3161.
p-C_7H_7	H	Ruhemann, *ibid.*, 1891, **24**, 3967.
·COOH	Me	Gabriel, *ibid.*, 1885, **18**, 2434.
Me	·CH_2·COOH	Gottlieb, *ibid.*, 1899, **32**, 959.

Phenolphthalein, which is a disubstituted phthalide, reacts with hydroxylamine at 80° to give an *N*-hydroxyphthalimidine : [1]

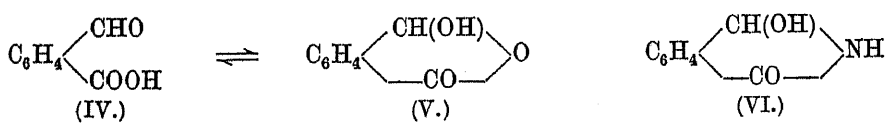


(Ar = *p*-OH·C_6H_4.)

The product undergoes a partial Beckmann change when heated with dilute H_2SO_4 and forms *p*-hydroxybenzoyl-*o*-benzoic acid. This reacts with aniline in the presence of $ZnCl_2$ at 180° :



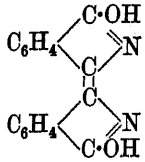
It might be expected that *o*-phthalaldehydic acid (IV) would react as hydroxy-phthalide (V)



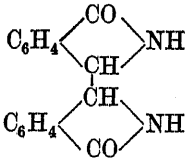
(IV.) (V.) (VI.)

[1] Orndorff and Murray, *J. A. C. S.*, 1917, **39**, 679.

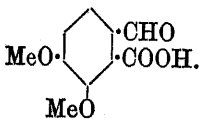
in a manner analogous to *o*-keto-acids. According to Bistrzycki and Liebermann,[1] however, the product with ammonia is not hydroxyphthalimidine (VI), but a mixture of VII and VIII.



(VII.)



(VIII.)



(IX.)

Wöhler's "opiammon,"[2] obtained by heating the ammonium salt of opianic acid (IX), is given a similar composition.

5. Preparation of phthalimides: $C_6<^{COOH}_{COOH} + NH_2R$, etc.

The methods available for the preparation of phthalimides may be grouped as follows:

(*a*) *From phthalic acid or anhydride and ammonia or primary amines.*—Phthalimide was first prepared by Laurent in 1836 by the distillation of ammonium phthalate:

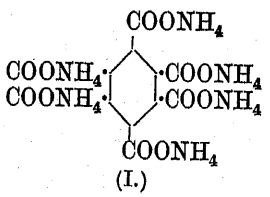
$$C_6H_4<^{COONH_4}_{COONH_4} \longrightarrow C_6H_4<^{CO}_{CO}>NH.$$

The best yield * is obtained by passing ammonia gas over molten phthalic anhydride at 140–160°[3]:

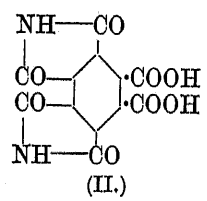
$$C_6H_4<^{CO}_{CO}>O + NH_3 \longrightarrow C_6H_4<^{CO}_{CO}>NH.$$

Phthalyl chloride is less suitable for the preparation of phthalimide itself, but is sometimes used for phthalanils.[4]

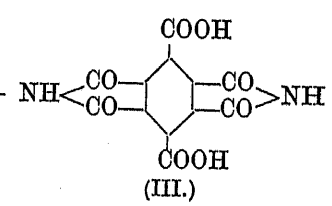
Ammonium mellitate (I) heated at 100–160° is converted into a mixture of the two euchronic acids (II and III) and the tri-imide, paramide (IV):[5]



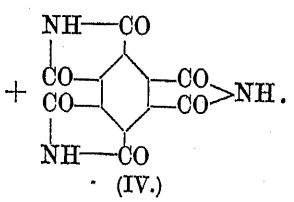
(I.)



(II.)



(III.)



(IV.)

[1] *Ber.*, 1893, **26**, 536. [2] *Ann.*, 1844, **50**, 6.

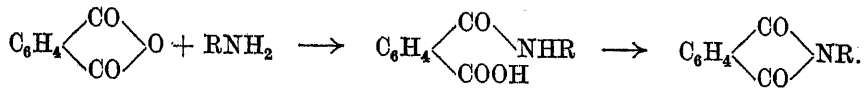
[3] Kuhara, *Amer. Chem. J.*, 1881, **3**, 27; Pucher and Johnson, *J. A. C. S.*, 1922, **44**, 820.

[4] Kuhara and Fukui, *Amer. Chem. J.*, 1901, **26**, 454; see also Dunlap and Cummer, *J. A. C. S.*, 1903, **25**, 612.

[5] Wöhler, *Ann.*, 1841, **37**, 269; Schwarz, *ibid.*, 1848, **66**, 49; cf. Mathews, *J. A. C. S.*, 1898, **20**, 648.

* A large-scale process is described in Austrian Patent 85380/1920.

N-Substituted phthalimides may be prepared by using primary amines in place of ammonia. The first product of the reaction is usually a phthalamic acid which passes into the phthalimide when heated alone or in a suitable solvent such as acetic acid : [1]



Hydroxylamine forms two isomeric " oximes " when heated with phthalic anhydride. Pratt [2] suggests that these are *syn*- and *anti*-forms of *iso*nitrosophthalide (V), but the *N*-hydroxyphthalimide structure (VI) is not excluded.[3]



(V.) (VI.)

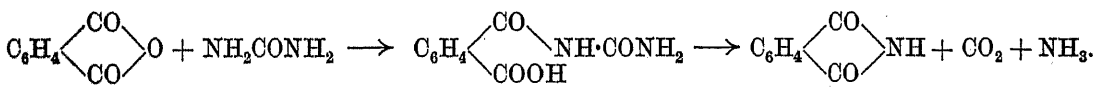
With hydrazines, either phthalazines (VII) or *N*-aminophthalimides (VIII) are produced.[4]



(VII.) (VIII.)

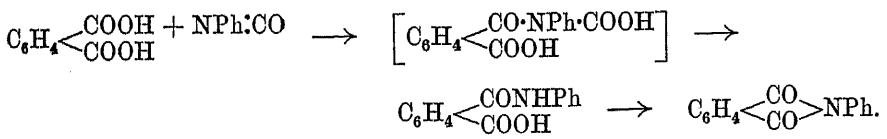
Semicarbazide yields only the phthalimide derivative (VIII, R = ·$CONH_2$).

(*b*) *Use of urea, etc., in place of ammonia.*—A convenient method of applying ammonia at high temperatures is to use urea or a similar ammonia derivative. From urea and phthalic anhydride Biedermann [5] obtained phthalimide. Piutti [6] showed that phthaluric acid is formed at 124°, which passes into phthalimide at 150–200° :



Similar results are obtained with thiourea, ammonium thiocyanate or ammonium carbonate. Phenylurea gives phthalanil.[7]

By the action of phenylcarbimide upon phthalic acid or anhydride Haller [8] obtained phthalanil. He suggested diphenylurea, PhNHCONHPh, as the intermediate product, but the following scheme seems equally probable :



[1] Rogow, *Ber.*, 1897, **30**, 1442; Pratt and Perkins, *J. A. C. S.*, 1918, **40**, 207, 216, 225, 1417.
[2] *Amer. Chem. J.*, 1912, **47**, 89; *Philipp. J. Science*, 1914, **8**, 165; **9**, 105.
[3] See Pratt and Miller, *J. A. C. S.*, 1918, **40**, 409, 412; Pratt and Young, *ibid.*, p. 1424.
[4] Dunlap, *ibid.*, 1905, **27**, 1091; Pratt and Young, *loc. cit.*
[5] *Ber.*, 1877, **10**, 1166.
[6] *Ann.*, 1882, **214**, 20.
[7] Tingle and Brenton, *J. A. C. S.*, 1910, **32**, 113.
[8] *Compt. rend.*, 1892, **114**, 1326.

Formamides may also be used with advantage, the formyl group being eliminated as CO and H_2O at the temperature of the reaction.[1]

(*c*) *From phthalamic acids.*—The conversion of phthalamic acids into the corresponding phthalimides by heating alone or in acetic acid has already been mentioned. The action of amines in bringing about a similar ring-closure has been studied by Tingle [2] and by Komatsu: [3]

$$C_6H_4\langle\begin{matrix}CO\cdot NHR\\COOH\end{matrix} + R'NH_2 \longrightarrow C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NR \text{ (or R')}.$$

Komatsu found that phthalanilic acid formed salts with methylamine, aniline, benzylamine and β-naphthylamine, from which phthalanil was obtainable by the action of heat or of acids or alkalis.

This was confirmed by Tingle and his co-workers for a number of phthalamic acids (R = *m*- or *p*-tolyl, β-naphthyl, *p*-chlorophenyl) and a variety of amines (aniline, ethylaniline, benzylamine, pyridine, quinoline). They also found that aniline and β-naphthylamine displaced the secondary amine from diphenyl- and di*iso*butyl-phthalamic acids:

$$C_6H_4\langle\begin{matrix}CO\cdot NR_2\\COOH\end{matrix} + ArNH_2 \longrightarrow C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NAr + R_2NH.$$

(R = Ph, $\cdot CH_2CHMe_2$; Ar = Ph, β-$C_{10}H_7$.)

Acetic acid is more reliable than amines for the conversion of phthalamic acids into phthalimides.[4] Boiling alcohol is sufficient in the case of 4-nitrophthalanilic acid.

The oxidation of triketo-*N*-methyl-tetrahydro*iso*quinoline to methylphthalimide [5] probably proceeds *via* the phthalamic acid:

$$C_6H_4\langle\begin{matrix}CO\cdot CO\\CO\cdot NMe\end{matrix} \xrightarrow{KMnO_4} \left[C_6H_4\langle\begin{matrix}COOH\\CO\cdot NHMe\end{matrix}\right] \longrightarrow C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NMe.$$

Rogow [6] obtained phthalanil by the action of glacial acetic acid upon phthalanilide:

$$C_6H_4\langle\begin{matrix}CONHPh\\CONHPh\end{matrix} \longrightarrow C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NPh + PhNH_2.$$

(*d*) *From nitriles.*—When diazotised anthranilic acid is treated with cuprous cyanide the product is not the expected *o*-cyanobenzoic acid but phthalimide: [7]

$$C_6H_4\langle\begin{matrix}COOH\\N_2Cl\end{matrix} \xrightarrow{Cu_2Cy_2} \left[C_6H_4\langle\begin{matrix}COOH\\C\equiv N\end{matrix}\right] \longrightarrow C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NH.$$

Similarly, the oxidation of *o*-cyanobenzylaniline by $KMnO_4$ in acetone gives phthalanil: [8]

$$C_6H_4\langle\begin{matrix}CH_2NHPh\\CN\end{matrix} \longrightarrow \left[C_6H_4\langle\begin{matrix}CO\cdot NHPh\\CN\end{matrix}\right] \longrightarrow C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NPh.$$

[1] Piutti, *Chem. Zing.*, 1885, **54**, 821; 1886, **55**, 839; Pratt and Perkins, *J. A. C. S.*, 1918, **40**, 205, 212; Tingle and Brenton, *loc. cit.*

[2] *Amer. Chem. J.*, 1907, **38**, 642; *J. A. C. S.*, 1908, **30**, 1882; 1909, **3**, 1157; 1910, **32**, 1319.

[3] *Zentr.*, 1909, ii, 983.

[4] Tingle and Bates, *J. A. C. S.*, 1910, **32**, 1319.

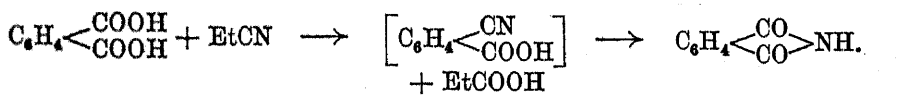
[5] Freund and Beck, *Ber.*, 1904, **37**, 1945.

[6] *Ibid.*, 1897, **30**, 1442.

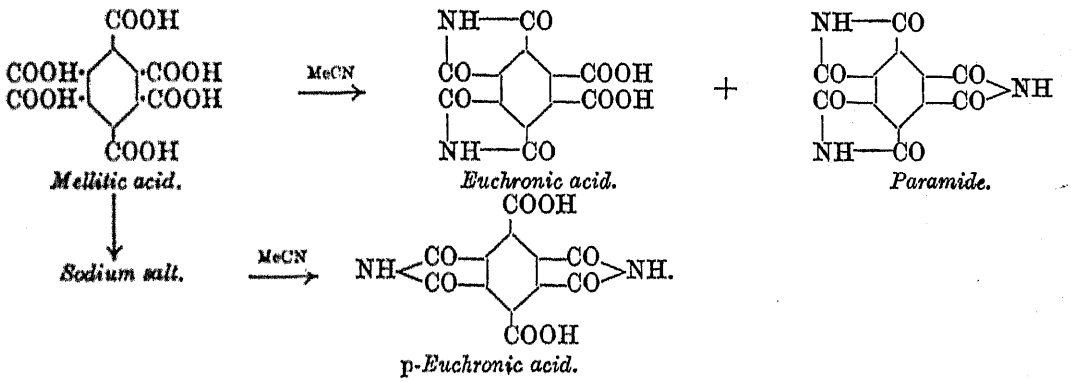
[7] Sandmeyer, *ibid.*, 1885, **18**, 1499; Tiemann and Müller, *ibid.*, 1886, **19**, 1478, 1498.

[8] Landsberger, *ibid.*, 1898, **31**, 2884.

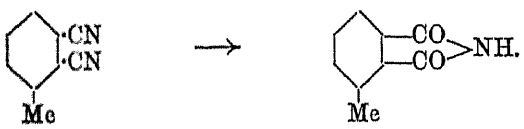
The interaction of organic acids with nitriles to form secondary acid amides has been applied by Mathews [1] to the preparation of phthalimides. Colby and Dodge [2] had found that interchange of ·CN and ·COOH groups occurred in certain cases when an aromatic acid was heated with an aliphatic nitrile, and this probably explains the 92% yield of phthalimide obtained by Mathews by heating phthalic acid with propionitrile at 180–200° :



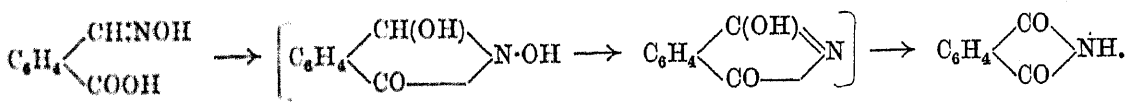
Phthalic acid and ethylene dicyanide give a mixture of phthalimide and succinimide. Acetonitrile is without action on phthalic acid, but with mellitic acid the two di-imides or the tri-imide are formed according to the conditions :



o-Dicyanobenzenes give phthalimides on hydrolysis. *E. g.* : [3]

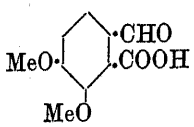


(*e*) *From oximes of o-aldehydobenzoic acids.*—Phthalimides are also formed by the action of alcoholic hydroxylamine upon *o*-aldehydobenzoic acids. The oxime first formed may be supposed to undergo condensation with the ·COOH group in somewhat the same way as the nitriles (which are dehydrated oximes). Racine [4] obtained phthalimide by heating the oxime of phthalaldehydic acid :

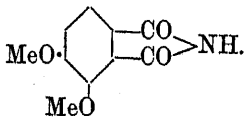


[1] *Amer. Chem. J.*, 1896, **18**, 679; 1898, **20**, 648.
[2] *Ibid.*, 1891, **13**, 1.
[3] Gabriel and Thieme, *Ber.*, 1919, **52**, 1082.
[4] *Ann.*, 1887, **239**, 85.

Opianic acid (IX) is converted by alcoholic NH_2OH into 3 : 4-dimethoxyphthalimide (X) : [1]



(IX.)



(X.)

Posner [2] obtained phthalimide by the action of alkali upon *o*-cyanobenzaldoxime :



Phthalimides have been prepared as follows :

(*a*) Action of amines upon phthalic acid, anhydride, ester or chloride.

(*b*) Action of urea, thiourea, substituted ureas, formamides, AmCNS or Am_2CO_3 upon phthalic anhydride.

(*c*) From phthalamic acids.

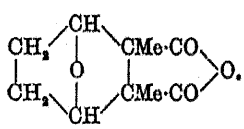
(*d*) From *o*-cyanobenzoic acid, *o*-dicyanobenzene or phthalic acid and nitriles.

(*e*) From oximes of *o*-aldehydobenzoic acid.

Base R·NH_2.	*Method* (*a*). *References.*	*Other Methods.* *References.*
Ammonia.	1, 3, 15, 19, 84, 126, 132	(*b*) 8, 17, 34, 38, 117, 124, 128 (*d*) 28, 39, 74, 82, 83 (*e*) 47, 80
Methylamine.		(*b*) 34 (*c*) 81, 101
Ethylamine.	11, 19	(*b*) 34 (*c*) 81
Propylamine.		(*c*) 81
*iso*Propylamine.		(*c*) 81
Butylamine.		(*c*) 81
δ-Phenoxybutylamine.	87	
Allylamine.		(*b*) 48, 62
Glycine.	25, 49	
α-Amino*iso*butyric acid.	113	
Leucine.	49	
β-Amino-β-phenylpropionic acid.	130	
Taurine.	52	
Benzylamine.		(*c*) 106
Aniline.	6, 16, 37, 76, 93, 97, 105, 114	(*b*) 57, 73, 110 (*c*) 73, 75, 79, 105, 109
o-Toluidine.	26, 29, 50, 93	(*c*) 29
m-Toluidine.	26	(*c*) 106, 108
p-Toluidine.	9, 26	(*c*) 29, 103, 106, 108
Mesidine.	20	
ψ-Cumidine.	26	
4-Amino-3-*iso*propyltoluene.	24	
p-Chloroaniline.	12	(*c*) 106, 108
p-Bromoaniline.	12	
p-Iodoaniline.	12	
p-Cyanoaniline.	116	
o-, *m*-, and *p*-Nitroanilines.	12, 66, 100, 119	

[1] Liebermann, *Ber.*, 1886, **19**, 2278, 2923.

[2] *Ibid.*, 1897, **30**, 1697.

Phthalic acid.	*Base.*	*References.*
Tetrabromophthalic acid.	Ammonia (formamide).	(*b*) 123
	Aniline.	(*a*) 123
	o-, *m*-, and *p*-Toluidines.	,,
	4-*o*-Xylidine.	,,
	ψ-Cumidine.	,,
	o-, *m*-, and *p*-Nitroanilines.	,,
	p-Bromoaniline.	,,
	p-Iodoaniline.	,,
	2 : 4-Dibromoaniline.	,,
	2 : 6-Dibromoaniline.	,,
	2 : 4 : 6-Tribromoaniline.	,,
	p-Aminophenol.	,,
	p-Aminoacetanilide.	,,
	o- and *p*-Phenetidines.	,,
	p-Aminoazobenzene.	,,
	Anthranilic acid.	,,
	α- and β-Naphthylamines.	,,
	Hydroxylamine.	,,
	Phenylhydrazine.	,,
	Phenylethylhydrazine.	,,
	2 : 4 : 6-Tribromophenylhydrazine.	,,
	3 : 4 : 6-Tri-iodophenylhydrazine.	,,
3 : 4-, 3 : 6-, and 4 : 5-Di-iodophthalic acid.	Aniline.	(*a*) 120
3 : 4 : 6-Tri-iodophthalic acid.	Aniline.	(*a*) 120
Tetraiodophthalic acid.	Ammonia (formaldehyde).	(*b*) 120
	Aniline.	
	o-, *m*-, and *p*-Toluidines.	
	m-Nitroaniline.	(*a*) 120
	p-Aminophenol.	
	p-Aminoacetanilide.	
	Phenylhydrazine.	(*a*) 122
3 : 4 : 5 : 6 3 : 6 : 4 : 5 4 : 5 : 3 : 6 — Dichlorodi-iodophthalic acids.	Aniline.	(*a*) 120
3 : 4-Dimethoxyphthalic acid (hemipinic).	Ammonia.	(*c*) 40 (*a*) 40
	Ethylamine.	(*a*) 72
	Benzylamine.	(*c*) 75
4 : 5-Dimethoxyphthalic acid (metahemipinic).	Ethylamine.	(*a*) 72
4-Sulphophthalic acid.	Ammonia.	(*a*) 43, 44, 131
4-Methylsulphonylphthalic acid.	Ammonia.	(*a*) 135
3-Nitrophthalic acid.	Aniline.	(*c*) 111
4-Nitrophthalic acid.	Aniline.	(*c*) 111
3-Nitro-6-hydroxy-5-methoxy-2-aldehydobenzoic acid.	Ammonia.	(*e*) 41
3-Carboxyphthalic acid.	Ammonia.	(*a*) 77
Mellitic acid.	Ammonia.	(*a*) 2, 5 (*d*) 83
	Aniline.	(*a*) 32
Cantharidine, 	Ammonia.	(*a*) 134

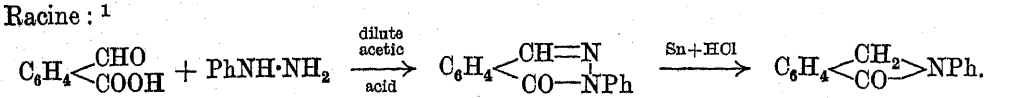
References.

[1] Laurent, *Ann.*, 1836, **19**, 47. [2] Wöhler, *ibid.*, 1841, **37**, 269. [3] Marignac, *ibid.*, 1842, **42**, 220. [4] Laurent, *ibid.*, 1846, **60**, 329. [5] Schwarz, *ibid.*, 1848, **66**, 46. [6] Laurent and Gerhardt, *ibid.*, **68**, 34. [7] Ladenburg, *Ber.*, 1876, **9**, 1527. [8] Biedermann, *ibid.*, p. 1670. [9] Michael, *ibid.*, 1877, **10**, 579. [10] Biedermann, *ibid.*, p. 1166. [11] Michael, *ibid.*, p. 1644. [12] Gabriel, *ibid.*, 1878, **11**, 2261. [13] Ballo, *Ann.*, 1879, **197**, 332. [14] Lassar Cohn, *ibid.*, 1880, **205**, 295, 300. [15] Kuhara, *Amer. Chem. J.*, 1881, **3**, 27.

[16] Döbner, *Ann.*, 1881, **210**, 267. [17] Piutti, *ibid.*, 1882, **214**, 19–24. [18] Wallach, *ibid.*, p. 248. [19] Landsberg, *ibid.*, **215**, 181, 196. [20] Eisenberg, *Ber.*, 1882, **15**, 1017. [21] Piutti, *ibid.*, 1883, **16**, 1322. [22] Lach, *ibid.*, p. 1781. [23] Schiff, *Ann.*, 1883, **218**, 194. [24] Kelbe and Warth, *ibid.*, **221**, 169. [25] Drechsel, *J. pr. Chem.*, 1883, **27**, 418. [26] Fröhlich, *Ber.*, 1884, **17**, 1802, 2679. [27] Pellizzari, *ibid.*, 1885, **18**, 216. [28] Sandmeyer, *ibid.*, p. 1499. [29] Piutti, *Ann.*, 1885, **227**, 205. [30] Vanni, *Gazz.*, 1885, **15**, 346. [31] Piutti, *ibid.*, p. 479. [32] Hötte, *J. pr. Chem.*, 1885, **32**, 238. [33] *Idem*, *ibid.*, **33**, 99. [34] Piutti, *Chem. Ztng.*, 1885, **54**, 821; 1886, **55**, 839. [35] Pellizzari, *Gazz.*, 1886, **16**, 205. [36] Just, *Ber.*, 1886, **19**, 1204. [37] Michael and Palmer, *ibid.*, p. 1375. [38] Aschan, *ibid.*, p. 1398. [39] Tiemann and Müller, *ibid.*, pp. 1478, 1497. [40] Liebermann, *ibid.*, pp. 2280, 2923. [41] Elbel, *ibid.*, p. 2306. [42] Hötte, *J. pr. Chem.*, 1886, **33**, 99; 1887, **35**, 281. [43] Rée, *Ann.*, 1886, **233**, 226, 238. [44] *Idem*, *J. C. S.*, 1886, **49**, 518. [45] Graebe, *Ann.*, 1887, **238**, 332. [46] Royer, *ibid.*, p. 355. [47] Racine, *ibid.*, **239**, 85. [48] Moiné, *Jahresber.*, 1886, 558; *Zentr.*, 1887, 39–40. [49] Reese, *Ann.*, 1887, **242**, 1. [50] Kuhara, *Amer. Chem. J.*, 1887, **9**, 51. [51] Maschke, *J. C. S.*, Abstr., 1887, 838. [52] Pellizzari and Matteucci, *Ann.*, 1888, **248**, 153, 157, 159. [53] Guareschi, *J. C. S.*, Abstr., 1888, 496. [54] Henriques, *Ber.*, 1888, **21**, 1616. [55] Winzer, *Ann.*, 1890, **257**, 309. [56] v. Niementowski, *Monatsh.*, 1891, **12**, 620. [57] Haller, *Compt. rend.*, 1892, **114**, 1326. [58] Young, *Ber.*, 1892, **25**, 2107. [59] Angeli, *ibid.*, 1893, **26**, 58. [60] Manasse, *ibid.*, p. 241. 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[82] Landsberger, *ibid.*, p. 2884. [83] Mathews, *J. A. C. S.* 1898, **20**, 648–668. [84] Edinger, *J. pr. Chem.*, 1899, **53**, 375. [85] Curtius and Davidis, *J. pr. Chem.*, 1899, **54**, 66–87; Foersterling, *Ber.*, 1895, **28**, Ref. 429. [86] Dobbie and Lauder, *J. C. S.*, 1899, **75**, 677. [87] Gabriel and Maas, *Ber.*, 1899, **32**, 1268. [88] Graebe and Buenzod, *ibid.*, p. 1992. [89] Oddo and Leonardi, *Gazz.*, 1899, **26**, i, 405. [90] v. Auwers and Schleicher, *Ann.*, 1899, **309**, 344. [91] Graebe and Gourwitz, *Ber.*, 1900, **33**, 2024. [92] Tafel and Eckstein, *ibid.*, 1901, **34**, 3277. [93] Kuhara and Fukui, *Amer. Chem. J.*, 1901, **26**, 454. [94] Gnehm and Gansser, *J. pr. Chem.*, 1901, **63**, 80. [95] Eibner and Merkle, *Ber.*, 1902, **35**, 2300. [96] Noyes and Warren, *Amer. Chem. J.*, 1902, **28**, 480. [97] Dunlap and Cummer, *J. A. C. S.*, 1903, **25**, 612. [98] D.R.-PP., 130680, 130681, 135836/1903. [99] Bredt, *Ann.*, 1903, **328**, 343. 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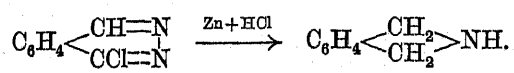
6. From phthalazines by reduction : $C_6<\begin{matrix}C{-}N\\C{-}N\end{matrix}$

The tetrahydrophthalazine ring is so unstable that it breaks down at once in the presence of the reducing agent, forming a dihydro*iso*indole and ammonia. This reaction was first observed by Racine : [1]

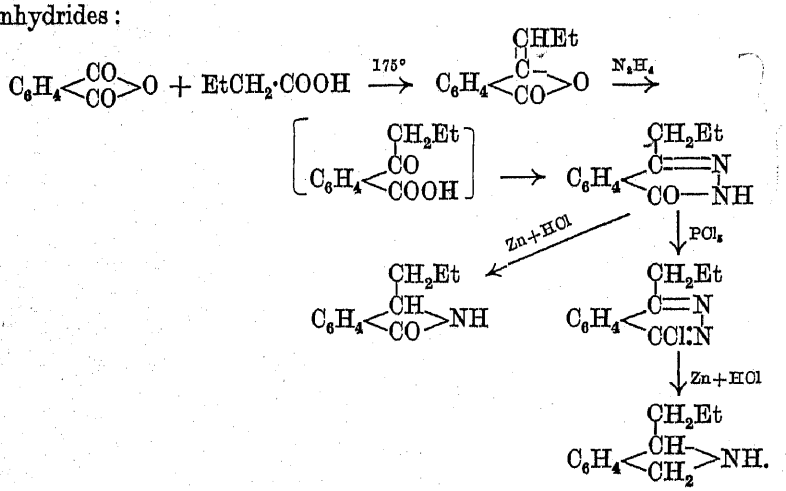


Phenylphthalimidine.

Phthalimidine itself was obtained in a similar manner from phthalazone by Gabriel and Neumann,[2] and the reaction has been extended to a number of other phthalazones and phthalazines by Gabriel and his co-workers. Chlorophthalazine (from phthalazone and PCl_5) is reduced to dihydro*iso*indole by zinc and HCl : [3]

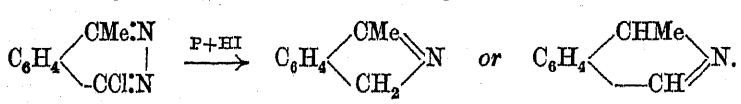


The phthalazones are readily prepared by the action of N_2H_4 upon alkylidene- and arylidene-phthalides obtained by Perkin's reaction from phthalic anhydride. Thus Bromberg [4] prepared 3-propylphthalimidine and 3-propyldihydro*iso*indole, starting from phthalic and butyric anhydrides :



The *iso*butyl and benzyl compounds were similarly prepared.

The reduction of methylchlorophthalazine with HI gives methyl*iso*indole.[5]



*iso*Indole itself has not been obtained.

[1] *Ann.*, 1887, **239**, 86. [2] *Ber.*, 1893, **26**, 524. [3] *Ibid.*, p. 526. [4] *Ibid.*, 1896, **29**, 1436.
[5] Gabriel and Neumann, *ibid.*, 1893, **26**, 711; Gabriel and Eschenbach, *ibid.*, 1897, **30**, 3029.

The following *iso*indole derivatives have been prepared from phthalazines :

(*a*) *Dihydroisoindoles*, $C_6H_4<^{CHR}_{CH_2}>NH$.

R = hydrogen (2, 6), methyl (3, 5), ethyl (7), propyl (4), *iso*butyl (4).

(*b*) *Phthalimidines*, $C_6H_4<^{CHR}_{CO}>NH$.

R = hydrogen (2), methyl (2), ethyl (7), propyl (4), *iso*butyl (8), benzyl (4).

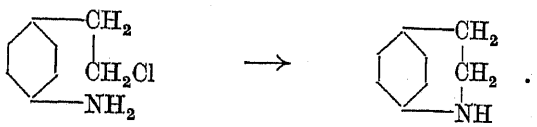
also $C_6H_4<^{CMe}_{CH_2}>N$ (3, 5) and $C_6H_4<^{CH_2}_{CO}>NPh$ (1).

References.

[1] Racine, *Ann.*, 1887, **239**, 86. [2] Gabriel and Neumann, *Ber.*, 1893, **26**, 524, 526. [3] *Idem*, *ibid.*, pp. 705, 708. [4] Bromberg, *ibid.*, 1896, **29**, 1435–1441. [5] Gabriel and Eschenbach, *ibid.*, 1897, **30**, 3029. [6] Fränkel, *ibid.*, 1900, **33**, 2808. [7] Daube, *ibid.*, 1905, **38**, 228. [8] Wölbling, *ibid.*, p. 3925.

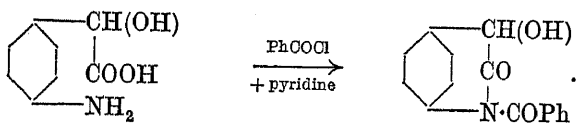
PARA-INDOLE

Although Kipping [1] and Manoukian [2] failed to obtain ring compounds from *meta*- and *para*-derivatives, v. Braun [3] found that *p*-aminophenylethyl chloride on dilution with ether is converted into " dihydro-*para*-indole " :



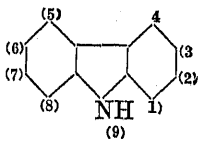
This remarkable compound very closely resembles dihydroindole. It has the same m. p., but a mixture of the two melts at a lower temperature.

Heller [4] has also obtained what appears to be a *para*-indole derivative by benzoylating *p*-aminomandelic acid in pyridine solution :



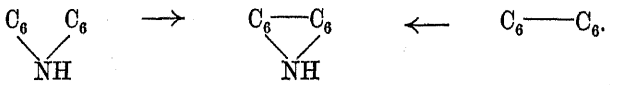
[1] *J. C. S.*, 1888, **53**, 21. [2] *Ber.*, 1901, **34**, 2082.
[3] *Ibid.*, 1912, **45**, 1274. [4] *Ibid.*, 1913, **46**, 280.

CHAPTER VI

CARBAZOLES, NAPHTHASTYRIL, ETC., 

Introductory

For the synthesis of carbazoles the starting-point may be (i) a diphenylamine derivative or (ii) a diphenyl derivative :



(i) *From diphenylamines.*—The dehydrogenation of diphenylamines to give *carbazoles* (sect. 1) occurs when the bases are passed through a hot tube or over an oxidising agent. The yields are naturally small, but in the anthraquinone series satisfactory results are obtained by alkaline fusion.

A better method is first to introduce sulphur by means of SCl_2 (or of sulphur with a catalyst) and then remove it by heating with copper or an oxidant (sect. 2).

β : β-Diphenylhydroxylamine, the *N*-hydroxy derivative of diphenylamine, is converted into carbazole by H_2SO_4 at $-20°$ (sect. 3). *o*-Hydroxydiphenylamine gives no carbazole, but *tetrahydrocarbazoles* are easily prepared by condensing arylamines with 2-chloro*cyclo*hexanone (sect. 4).

*cyclo*Hexanones are more conveniently converted into *tetrahydrocarbazoles* by the Drechsel–von Baeyer method (sect. 5), which is precisely analogous to Fischer's indole synthesis. This important method has been applied to the preparation of a large number of tetrahydrocarbazoles, and from the latter *carbazoles* are readily obtained by dehydrogenation with sulphur or lead oxide. Bucherer's method (sect. 5) is a modification, in effect, of the Drechsel–von Baeyer synthesis and leads to *naphthocarbazoles.*

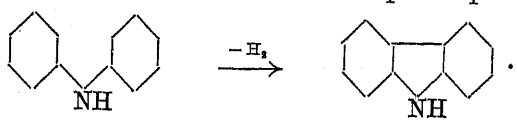
The smooth elimination of nitrogen from arylaziminobenzenes provides another important *carbazole* synthesis (sect. 6).

(ii) *From diphenyls.*—*o*-Aminodiphenyl loses two hydrogen atoms when strongly heated and gives *carbazole* (sect. 7), but much more satisfactory results are obtained from 2 : 2′-diaminodiphenyl (sect. 8), either by elimination of NH_3, as in Ladenburg's pyrrolidine and piperidine syntheses, or by tetrazotisation.

The amino groups may be introduced by the action of ammonia upon 2 : 2′-dihydroxydiphenyl derivatives (sect. 9), when ring-closure follows in the same operation.

1. From diphenylamines: $C_6{<}_{NH}{>}C_6$

Diphenylamine is converted into carbazole when its vapour is passed through a hot tube.[1]



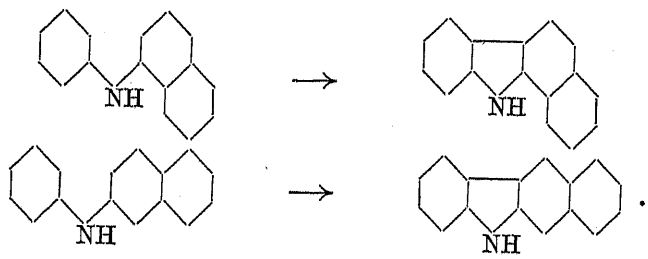
The yield is only about 5%, but much diphenylamine is recovered unchanged. The hydrogen is used up in reducing the diphenylamine to aniline, benzene and NH_3.

Carbazole is also formed in small amount in the pyrogenous production of diphenylamine from aniline,[2] and from benzene and NH_3 or acetylene and NH_3.[3] A similar dehydrogenation of diphenylamine accounts for the formation of carbazole when induline is distilled with lime.[4]

N-Methyldiphenylamine gives, not methylcarbazole, but carbazole and methane.[5]

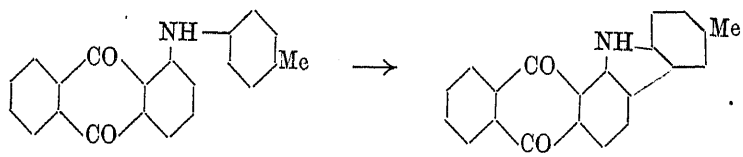
Walther[6] claims the production of carbazole by passing diphenylamine vapour and air over V_2O_5.

Phenyl-α- and -β-naphthylamines undergo a similar dehydrogenation when their vapours are led through a hot tube.[7]



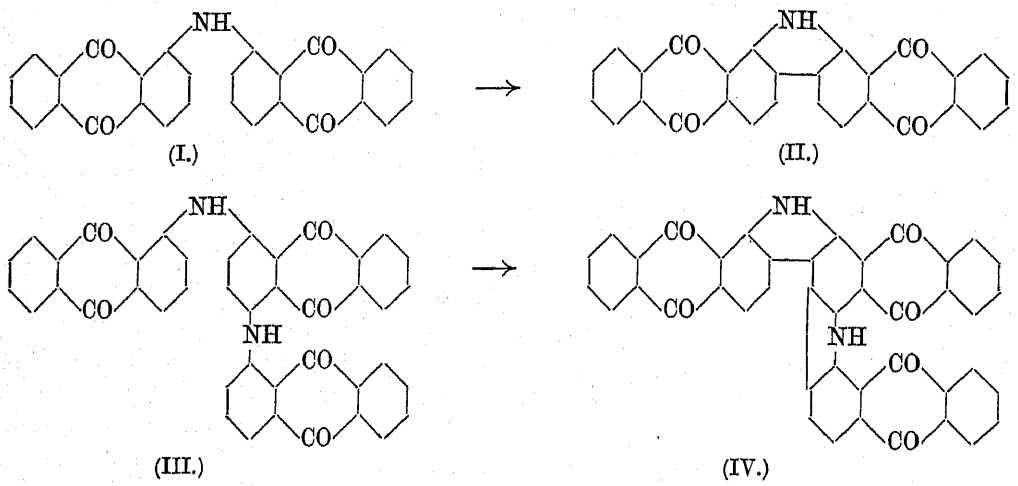
The formation of the *linear* naphthocarbazole from phenyl-β-naphthylamine is exceptional. No trace of the α-β- (" angular ") compound is obtained.[8]

In the anthraquinone series phthaloyl- and diphthaloyl-carbazoles are obtained from arylamino-anthraquinones or anthrimides either by oxidation, by alkaline fusion or by the action of $AlCl_3$, etc. In the case of arylaminoanthraquinones the *para* position must be occupied by methyl or chlorine to prevent the formation of diphenyl (*i.e.* benzidine) derivatives. Thus:[9]



[1] Graebe, *Ber.*, 1872, **5**, 376; *Ann.*, 1873, **167**, 125; 1874, **174**, 177; Meyer and Hofmann, *Monatsh.*, 1916, **37**, 682, 705.
[2] Hofmann, *Jahresber.*, 1862, **235**; Graebe, *Ann.*, 1873, **167**, 125; Braun and Grieff, *Ber.*, 1872, **5**, 276; Löb, *ibid.*, 1901, **34**, 918; Meyer and Tanzen, *ibid.*, 1914, **46**, 3183; Meyer and Wesche, *ibid.*, 1917, **50**, 440.
[3] Meyer and Tanzen, *Ann.*, 1913, **46**, 3187. [4] Witt, *ibid.*, 1887, **20**, 1541.
[5] Graebe, *ibid.*, 1874, **7**, 49; *Ann.*, 1874, **174**, 181. [6] D.R.-P. 168291.
[7] Graebe and Knecht, *Ann.*, 1880, **202**, 16. [8] Kehrmann, Oulevay and Regis, *Ber.*, 1913, **46**, 3712.
[9] D.R.-P. 288824.

The alkaline fusion of 1 : 1′-dianthrimide (I) [1] and 1 : 1′ : 4′ : 5″-trianthrimide (III) [2] gives carbazoles (II and IV) :

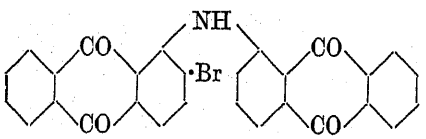


(I.) (II.)

(III.) (IV.)

The same condensation is brought about by the action of $AlCl_3$ [3] or $FeCl_3$.[4]

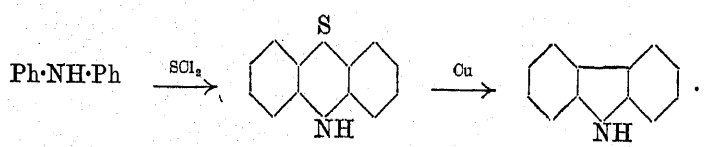
2-Bromo-1 : 1′-dianthrimide (V) is converted into a carbazole (II) by the action of $AlCl_3$ or of a mixture of potassium acetate and cuprous iodide.[5]



(V.)

2. From thiodiphenylamine : $C_6<\begin{matrix}S\\NH\end{matrix}>C_6$

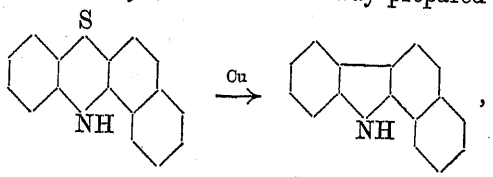
When diphenylamine is heated with sulphur dichloride [6] or with sulphur and $AlCl_3$ [7] it gives thiodiphenylamine, from which the sulphur may be readily removed by heating with copper at 240° :



Dithiodiphenylamine (from diphenylamine and S_2Cl_2) behaves similarly.[8]

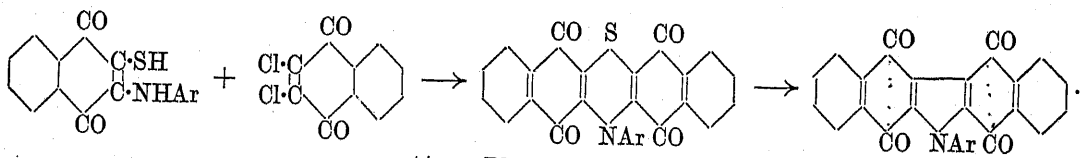
[1] D.R.-P. 230407. [2] D.R.-P. 208969. [3] D.R.-PP. 240080, 249000, 262788.
[4] D.R.-P. 251350. [5] D.R.-P. 267522.
[6] Goske, *Ber.*, 1887, **20**, 232; Holzmann, *ibid.*, 1888, **21**, 2064. [7] D.R.-P. 222879.
[8] Holzmann, *Ber.*, 1888, **21**, 2064.

From phenyl-α-naphthylamine Kym [1] in the same way prepared a naphthocarbazole :



and Ris [2] obtained dinaphthocarbazole in 55% yield from thio-β : β-dinaphthylamine.

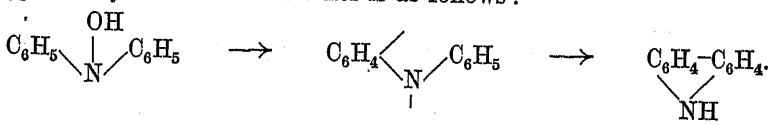
A linear dinaphthocarbazole has recently been prepared by Fries and Ochwat,[3] the corresponding thiodinaphthylamine being desulphurised by heating in nitrobenzene or in glacial acetic acid with a little nitric acid :



(Ar = Ph or *p*-Cl·C_6H_4.)

3. From diphenylhydroxylamine : $C_6{>}N{<}C_6$

Wieland and Müller [4] prepared diphenylhydroxylamine from nitrosobenzene and phenyl magnesium bromide. Treated with a mixture of conc. H_2SO_4 and acetic acid at −20° the product is converted into carbazole (25% yield). *o*-Hydroxydiphenylamine is not formed intermediately, for no trace of carbazole can be obtained from this compound under the same conditions. The mechanism suggested by Wieland and Müller is as follows :

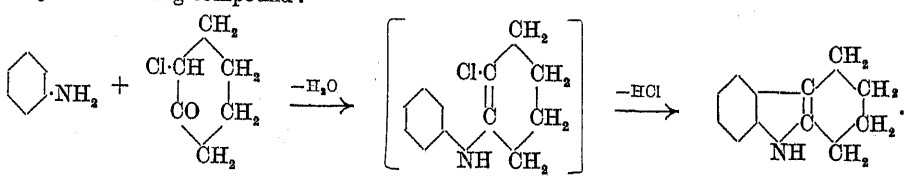


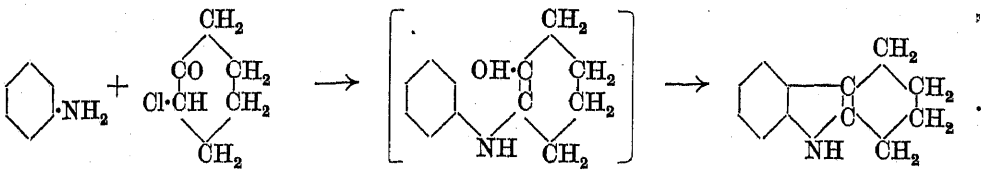
4. From *o*-hydroxydiphenylamine : $C_6{<}^{OH}_{N}{>}C_6$

Although *o*-hydroxydiphenylamine shows no tendency to anhydrise to carbazole,[5] tetrahydrocarbazoles are obtained quantitatively * by heating together a mixture of arylamine and 2-chloro*cyclo*hexanone at 150–160° : [6]

[1] *Ber.*, 1890, **23**, 2465. [2] *Ibid.*, 1886, **19**, 2242. [3] *Ibid.*, 1923, **56**, 1298.
[4] *Ibid.*, 1913, **46**, 3304. [5] Wieland and Müller, *loc. cit.* [6] D.R.-P. 374098/1923.

* An alternative explanation avoids the improbability of an *o*-hydroxydiphenylamine being converted quantitatively into the ring-compound :

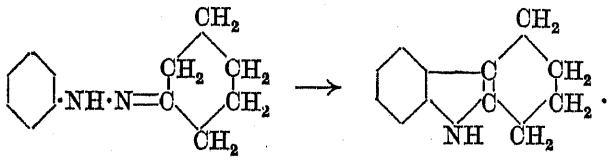




The reaction has been applied to aniline, ethylaniline and *o*- and *p*-toluidines.

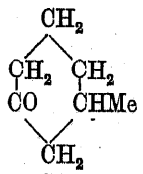
5. From arylhydrazones of cyclic ketones: C_6—N—C_6

The Fischer indole synthesis was first applied to the carbazole group by Drechsel,[1] who heated *cyclo*hexanone with phenylhydrazine and obtained a product identified six years later by v. Baeyer [2] as tetrahydrocarbazole:

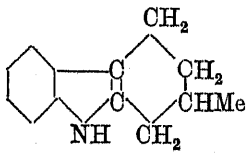


The phenylhydrazones of *cyclo*hexanone-3-carboxylic acid [3] and the isomeric 4-carboxylic acid [4] behave similarly when heated with HCl.

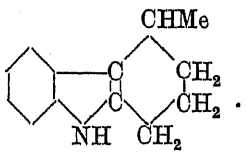
From 3-methyl*cyclo*hexanone (I) Plancher and Carrasco [5] obtained the expected isomeric methyltetrahydrocarbazoles (II and III) by the action of alcoholic $ZnCl_2$ upon the phenylhydrazone:



(I.)



(II.)

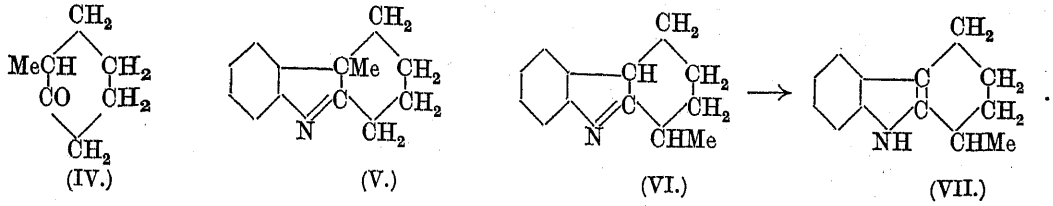


(III.)

More interesting is the behaviour of *cyclo*hexanones carrying an *ortho* substituent. 2-Methyl-*cyclo*hexanone (IV) was shown by Plancher and Testoni [6] to give two products—one the ordinary tetrahydrocarbazole (VII), the other a tetrahydrocarbazolenine (V). It seems probable that the

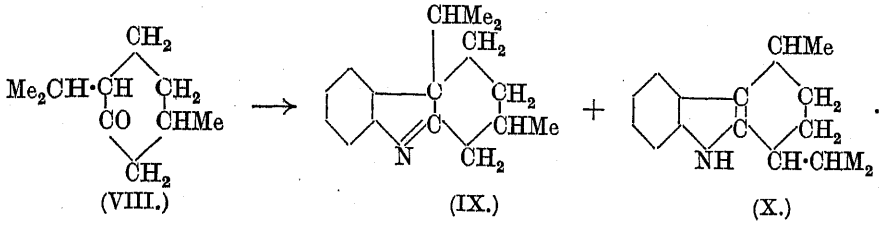
[1] *J. pr. Chem.*, 1888, **38**, 69.
[2] *Ann.*, 1894, **278**, 105.
[3] v. Baeyer and Tutein, *Ber.*, 1889, **22**, 2183.
[4] Perkin, *J. C. S.*, 1904, **85**, 428.
[5] *R. A. L.*, 1904, [v], **13**, i, 632.
[6] *Gazz.*, 1900, **30**, ii, 558; *R. A. L.*, 1900, [v], **9**, i, 218.

primary products are two tetrahydrocarbazolenines (V and VI), of which only one is capable of rearrangement to the tetrahydrocarbazole (VII):



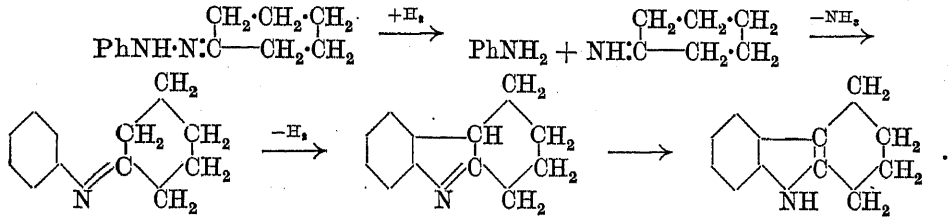
(IV.) (V.) (VI.) (VII.)

Menthone (VIII) similarly gives two products (IX and X):

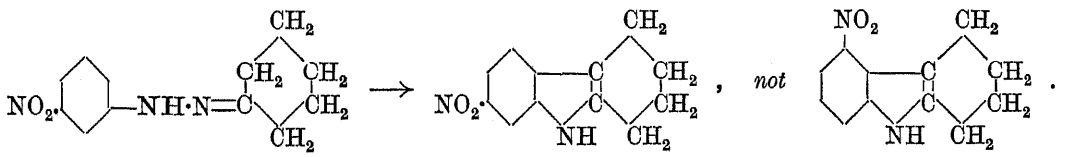


(VIII.) (IX.) (X.)

These results are in accordance with Reddelien's view of the Fischer indole synthesis (see p. 95), according to which the reaction takes the following course:



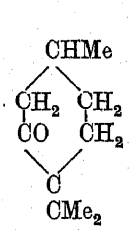
The Drechsel synthesis has been subjected to a very full investigation by Borsche, Witte and Bothe,[1] who obtained good yields by simply heating the hydrazones (unpurified) with dil. H_2SO_4 on the water-bath. It was shown that *m*- and *p*-substituents in the phenylhydrazine nucleus did not hinder carbazole formation, and in the former case the diphenyl linkage took place *para* (not *ortho*) to the *meta* substituent. Thus:



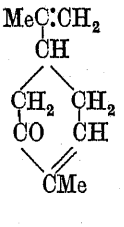
The reaction is limited, however, to the simpler *cyclo*hexanones, and no carbazole derivative

[1] *Ann.*, 1908, **359**, 49–80.

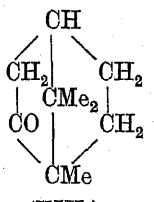
could be obtained from pulegone (XI), carvone (XII), camphor (XIII) or Δ^2-3 : 5-dimethyl*cyclo*hexenone (XIV).



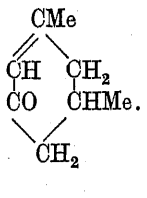
(XI.)



(XII.)



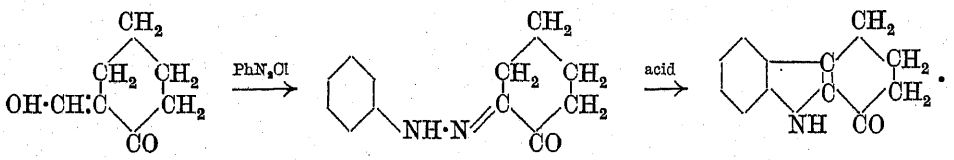
(XIII.)



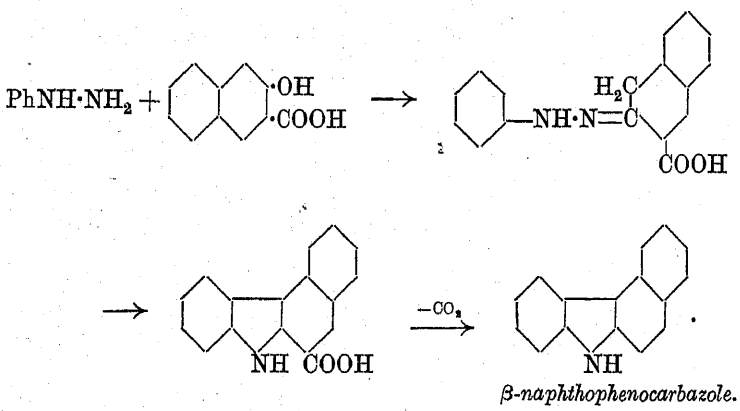
(XIV.)

The tetrahydrocarbazoles are readily converted into carbazoles by distillation over lead oxide, or, better, by oxidation with mercuric acetate or by boiling with the theoretical amount of sulphur.

The phenylhydrazone of *cyclo*hexan-1 : 2-dione was prepared by Coffey [1] by the action of diazobenzene upon hydroxymethylene*cyclo*hexanone. It gives the corresponding ketotetrahydrocarbazole in good yield, but the product is difficult to purify :



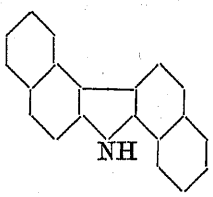
In the naphthalene series the α- and β-hydroxy-compounds may function under certain conditions as ketones, condensing with hydrazines to give hydrazones from which naphthocarbazoles may be obtained. Schöpff's preparation of β-naphthophenocarbazole from β-hydroxynaphthoic acid and phenylhydrazine [2] may thus be explained :



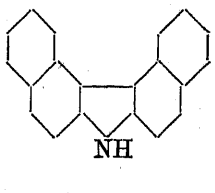
β-naphthophenocarbazole.

[1] *Rec. trav. chim.*, 1923, **42**, 531. [2] *Ber.*, 1896, **29**, 265; Japp and Maitland, *J. C. S.*, 1903, **83**, 267.

The same product was obtained from β-naphthol by Japp and Maitland,[1] who also condensed β-naphthol with α- and β-naphthylhydrazines to give dinaphthocarbazoles (30% yield):

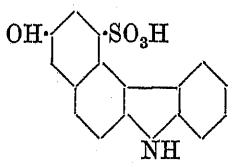


βα.

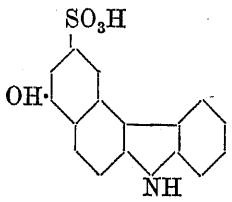


ββ.

The yields are much improved (especially in the β-series) by the use of the Bucherer bisulphite reaction.[2] Thus from β-naphthol by the action of phenylhydrazine and aqueous sodium bisulphite 46% of the theoretical yield of β-naphthophenocarbazole is obtained, and from 2:3-hydroxynaphthoic acid the yield is 70%. Sulphonated β-naphthols behave similarly, but β-naphthol derivatives react less smoothly. The naphthylamines and their sulphonic acids react in the same way as the corresponding naphthols. In the aminonaphtholsulphonic acids, J- and γ-, the ·OH group is protected by a *meta* SO_3H group and only the ·NH_2 enters into reaction. The products are:

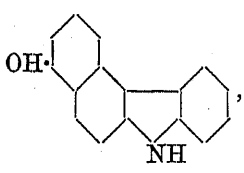


From γ-acid.

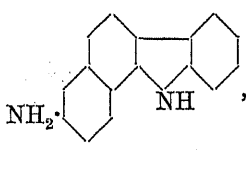


From J-acid.

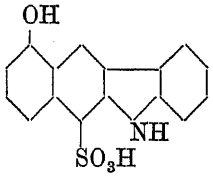
In A-acid (2:5:1-aminonaphtholsulphonic acid) both the ·OH and the ·NH_2 are free to react. Moreover, the easy elimination of the -sulphonic acid group leads to 2:1- as well as 2:3-carbazoles. Bucherer and Wahl[3] obtained evidence for at least four products in this case, viz.:



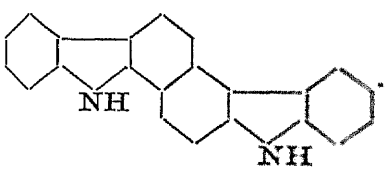
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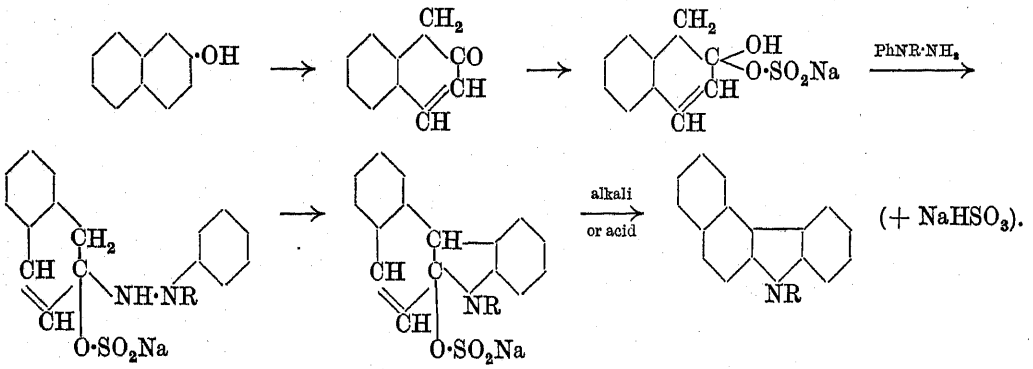
and



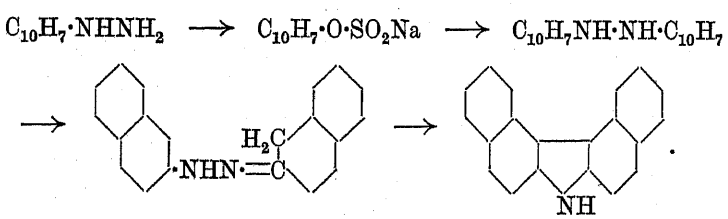
Friedländer[4] has shown that not only phenylhydrazine but *as*-alkylphenylhydrazines, PhNR·NH_2

[1] *Loc. cit.*
[2] D.R.-P. 208960; Bucherer and Seyde, *J. pr. Chem.*, 1908, **77**, 403; Bucherer and Wahl, *ibid.*, 1922, **103**, 272, 273; Bucherer and Zimmermann, *ibid.*, 1922, **103**, 294–304.
[3] *Loc. cit.*
[4] *Chem. Ztng.*, 1916, **40**, 918; *Ber.*, 1921, **54**, 620.

(where R = Me or Et), condense with β-naphthol or 2 : 3-hydroxynaphthoic acid in the presence of bisulphite, giving *N*-alkyl carbazoles :

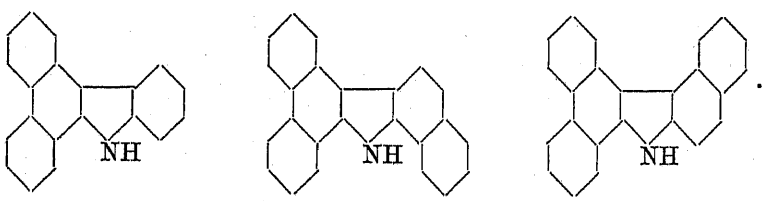


The action of bisulphite upon naphthylhydrazines has been investigated by Bucherer and Schmidt.[1] A "sulphurous ester" is first formed, which reacts with a further quantity of naphthylhydrazine to give a hydrazonaphthalene. This then undergoes transformation into a dinaphthocarbazole :



The yields are higher in the β-series than in the α-series.

Phenanthrocarbazoles were prepared by Japp [2] from phenanthrol by heating with phenyl- and α- or β-naphthyl-hydrazines at 200° :



From phenylhydrazine. *From α-naphthylhydrazine.* *From β-naphthylhydrazine.*

The Drechsel method or its modifications has been used in the following cases :

(a) *Phenylhydrazine condensed with :*	*References.*
*cyclo*Hexanone.	1, 3, 18
*cyclo*Hexanone-3-carboxylic acid.	2
*cyclo*Hexanone-4-carboxylic acid.	8
2-Methyl*cyclo*hexanone.	6

[1] *J. pr. Chem.*, 1909, **79**, 369.
[2] Japp and Findlay, *J. C. S.*, 1897, **71**, 1124; Japp and Maitland, *ibid.*, 1903, **83**, 267.

	References.
3-Methyl*cyclo*hexanone.	9, 10
Menthone.	9, 10
Pulegone (fails).	10
Carvone (fails).	10
Δ^2-3 : 5-Dimethyl*cyclo*hexenone (fails).	10
α-Naphthol.	11, 12
α-Naphthol-4-sulphonic acid (N. W. acid).	11, 12
β-Naphthol.	7, 11, 12
2 : 3-Hydroxynaphthoic acid (loses CO_2).	4, 7, 11, 12
β-Naphthol-8-sulphonic acid (Crocein acid).	19, 20
β-Naphthol-3 : 6-disulphonic acid (R-acid).	11, 12
β-Naphthol-6 : 8-disulphonic acid (G-acid).	11, 12
2 : 5 : 7-Aminonaphtholsulphonic acid (J-acid).	16, 19, 20
2 : 6 : 8-Aminonaphtholsulphonic acid (γ-acid).	16, 19, 20
2 : 5 : 1-Aminonaphtholsulphonic acid (A-acid).	19
2: 5 : 1 : 7-Aminonaphtholdisulphonic acid.	19
Phenanthrol.	5, 7
*cyclo*Hexan-1 : 2-dione.*	21

(*b*) cyclo*Hexanone condensed with the following hydrazines :*

Phenylhydrazine.	1, 3, 18
o-, *m*-, and *p*-Nitrophenylhydrazines.	10
o- and *p*-Chlorophenylhydrazines.	10
p-Bromophenylhydrazine.	10
p-Acetaminophenylhydrazine.	18
m-Oxalaminophenylhydrazine.	22
2-Chloro-5-nitrophenylhydrazine.	18
p-Tolylhydrazine.	10
p-Anisylhydrazine.	10
p-Phenetylhydrazine.	10
α- and β-Naphthylhydrazines.	10
p : *p*′-Dihydrazinodiphenylmethane.	14
Phenylmethylhydrazine.	18
p-Acetaminophenylmethylhydrazine.	18
α-Phenylhydrazino-acetic ester ($PhN(NH_2)\cdot CH_2\cdot COOEt$).	23
1-Aminodihydro-3-quinoxalone $\left(C_6H_4\langle \begin{matrix} NH\text{——}CO \\ N(NH_2)\cdot CH_2 \end{matrix}\right)$.	23

(*c*) *Other hydrazines and cyclic ketones* :

Hydrazine.	*Ketone.*	
p-Tolylhydrazine.	*d*-3-Methyl*cyclo*hexenone.	10
4-*m*-Xylylhydrazine.	,, ,,	10
ψ-Cumylhydrazine.	,, ,,	10
m-Nitrophenylhydrazine.	,, ,,	10
Phenylmethylhydrazine. } Phenylethylhydrazine. }	β-Naphthol.	15, 17
		15, 17
α-Naphthylhydrazine.	β-Naphthol.	7
	Phenanthrol.	5, 7
β-Naphthylhydrazine.	β-Naphthol.	7
	Phenanthrol.	5, 7

(*d*) *Action of sodium bisulphite upon* :

α- and β-Naphthylhydrazines.	13

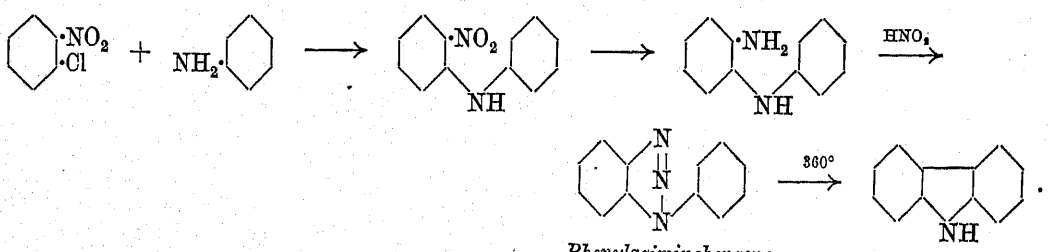
* See p. 170.

References.

[1] Drechsel, *J. pr. Chem.*, 1888, **38**, 69. [2] v. Baeyer and Tutein, *Ber.*, 1889, **22**, 2183. [3] v. Baeyer, *Ann.*, 1894, **278**, 105. [4] Schöpff, *Ber.*, 1896, **29**, 265. [5] Japp and Findlay, *J. C. S.*, 1897, **71**, 1124. [6] Plancher and Testoni, *Gazz.*, 1900, **30**, ii, 558; *R. A. L.*, 1900, [v], **9**, i, 218. [7] Japp and Maitland, *J. C. S.*, 1903, **83**, 267. [8] Perkin, *ibid.*, 1904, **85**, 428. [9] Plancher and Carrasco, *R. A. L.*, 1904, [v], **13**, i, 632. [10] Borsche, Witte and Bothe, *Ann.*, 1908, **359**, 49–80. [11] D.R.-P. 208960. [12] Bucherer and Seyde, *J. pr. Chem.*, 1908, **77**, 403. [13] Bucherer and Schmidt, *ibid.*, 1909, **79**, 369. [14] Borsche and Kienitz, *Ber.*, 1910, **43**, 2336. [15] Friedländer, *Chem. Ztng.*, 1916, **40**, 918. [16] König and Haller, *J. pr. Chem.*, 1920, **101**, 38. [17] Friedländer, *Ber.*, 1921, **54**, 620. [18] Perkin and Plant, *J. C. S.*, 1921, **119**, 1831. [19] Bucherer and Wahl, *J. pr. Chem.*, 1922, **103**, 272. [20] Bucherer and Zimmermann, *ibid.*, p. 294. [21] Coffey, *Rec. trav. chim.*, 1923, **42**, 531. [22] Edwards and Plant, *J. C. S.*, 1923, **123**, 2398. [23] Perkin and Riley, *ibid.*, p. 2401.

6. From arylaziminobenzenes : $C_6{=}N_3{-}C_6$

This important synthesis is due to Graebe and Ullmann,[1] who obtained carbazole quantitatively by distillation of the diazoimide from *o*-aminodiphenylamine :

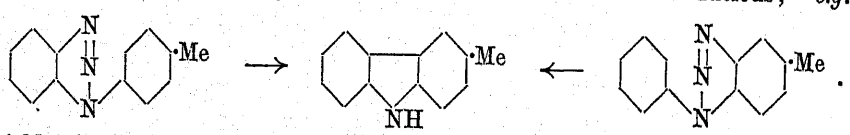


Phenylaziminobenzene.

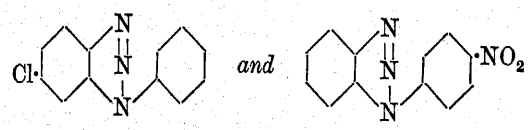
A carboxyl group [2] or sulphonic group [3] *para* to the ·NH· of the diphenylamine facilitates the preparation of the intermediates required and is completely eliminated as CO_2 or SO_2 during the last stage of the synthesis.

Arylaziminobenzenes in which the aryl substituent carries an *ortho* methyl group give acridines as by-products [4] (see p. 381).

Substituted carbazoles may usually be obtained equally well by two methods, the substituent being introduced either into the aryl nucleus or into the aziminobenzene nucleus ; [5] *e.g.*

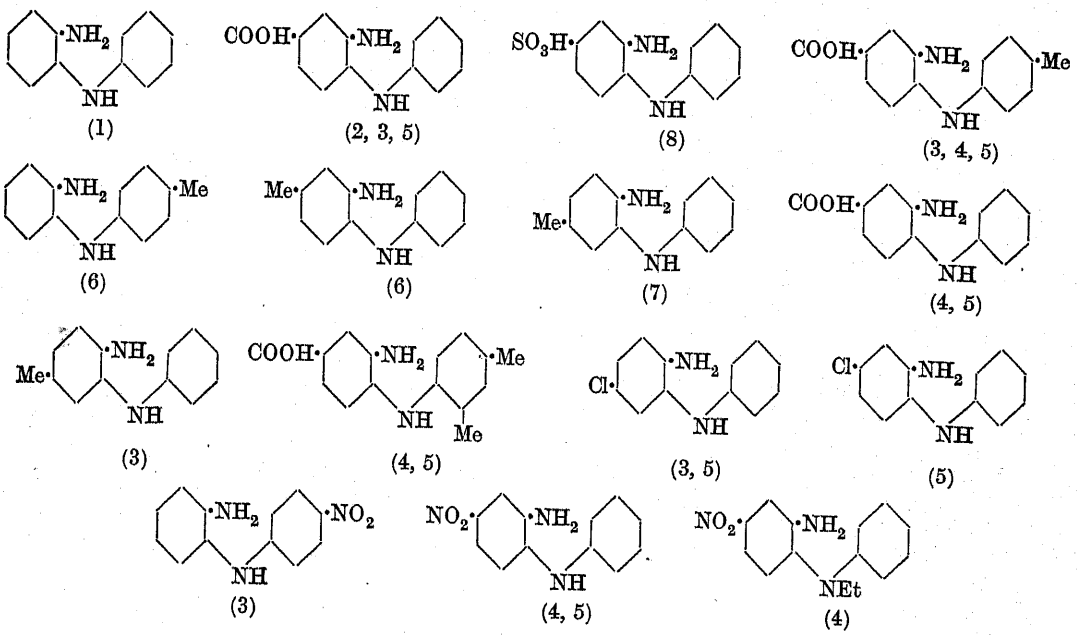


The yields of carbazoles from



[1] *Ann.*, 1896, **291**, 16. [2] Ullmann, *Ber.*, 1898, **31**, 1697.
[3] Schwalbe and Wolff, *ibid.*, 1911, **44**, 237.
[4] Delétra and Ullmann, *Zentr.*, 1904, i, 1568; Ullmann, *Ann.*, 1904, **332**, 82.
[5] Borsche and Feise, *Ber.*, 1907, **40**, 382.

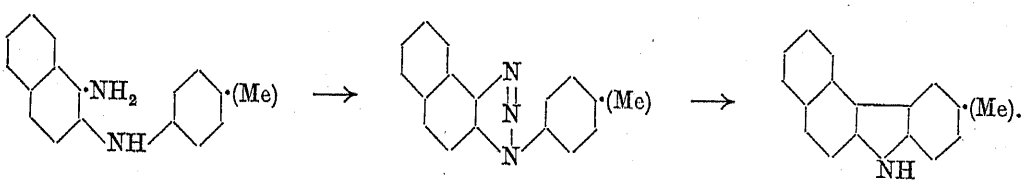
are not good,[1] but in most other cases the reaction is almost quantitative. Carbazoles have been prepared by this method from the following diphenylamine derivatives :



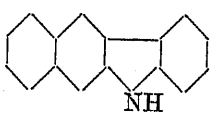
References.

[1] Graebe and Ullmann, *Ann.*, 1896, **291**, 16. [2] Ullmann, *Ber.*, 1893, **31**, 1697. [3] *Idem, ibid.*, 1900, **33**, 1697. [4] Delétra and Ullmann, *Zentr.*, 1904, i, 1568. [5] Ullmann, *Ann.*, 1904, **332**, 82–104. [6] Borsche and Feise, *Ber.*, 1907, **40**, 382. [7] Borsche, Witte and Bothe, *Ann.*, 1908, **359**, 75. [8] Schwalbe and Wolff, *Ber.*, 1911, **44**, 237.

In the naphthalene series phenyl- and *p*-tolyl-aziminonaphthalenes have been converted into naphthocarbazoles : [2]

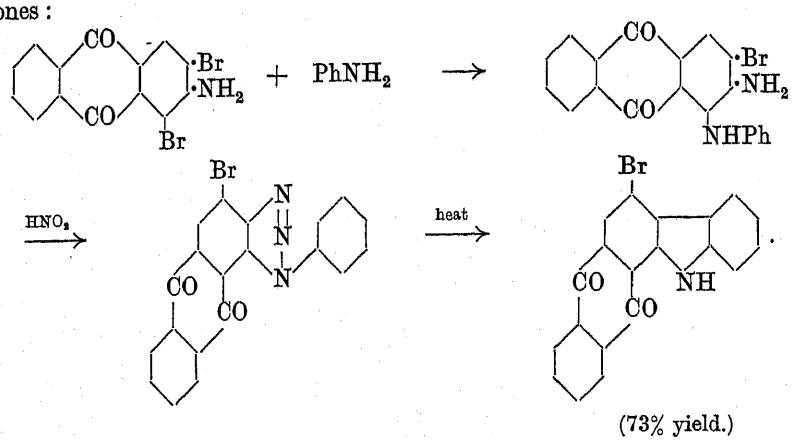


Kehrmann, Oulevay and Regis [3] showed that by the distillation of phenylaziminonaphthalene there is formed, in addition to the *ang.*-naphthocarbazole, a small amount of the *linear* body (see also p. 165) :



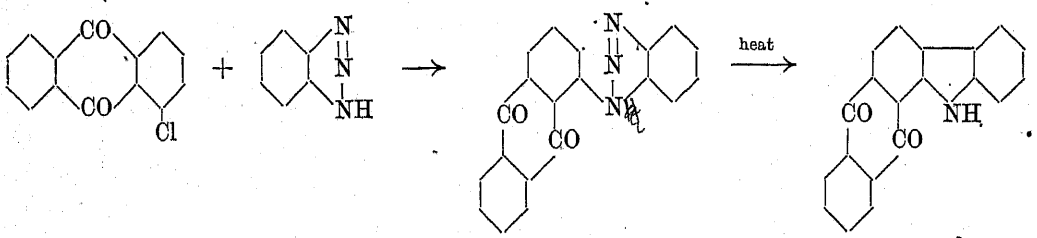
[1] Ullmann, *Ber.*, 1900, **33**, 1697.
[2] *Idem, ibid.*, p. 1697; *Ann.*, 1904, **332**, 101, 103.
[3] *Ber.*, 1913, **46**, 3712.

Ullmann and Illgen [1] extended the reaction to the synthesis of 1 : 2-phthaloylcarbazoles from anthraquinones :



(73% yield.)

α-Anthraquinonylaziminobenzene was also prepared from α-chloroanthraquinone and aziminobenzene (benzotriazole) :

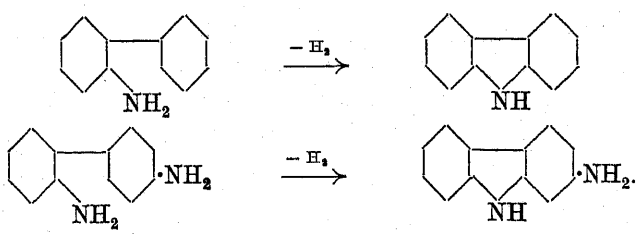


(70% yield.) (77% yield.)

The products dye cotton pale brown and pale orange respectively from the vat.

7. From *o*-aminodiphenyls : $C_6—C_6$ / NH_2

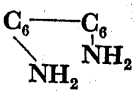
o-Aminodiphenyl gives carbazole when heated to redness with lime,[2] while 2 : 4′-diaminodiphenyl gives 2-aminocarbazole :



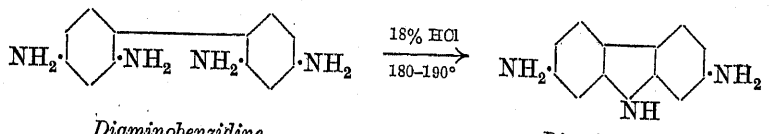
Diphenyline.

[1] *Ber.*, 1914, **47**, 380.

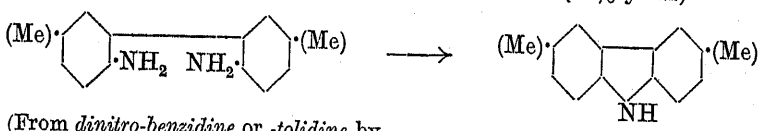
[2] Blank, *ibid.*, 1891, **24**, 306.

8. From 2 : 2′-diaminodiphenyl, etc. : 

The usual ring-closure with elimination of NH_3 occurs when *o* : *o*′-diaminodiphenyl or its derivatives is heated with 15–20% HCl or 25% H_2SO_4 at about 200° : [1]

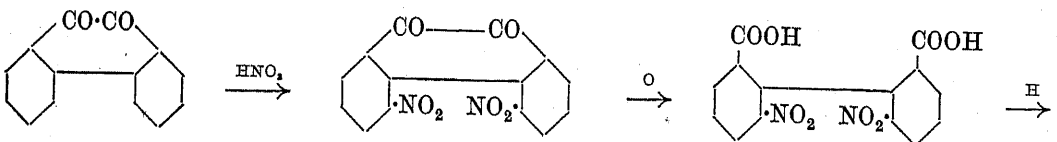


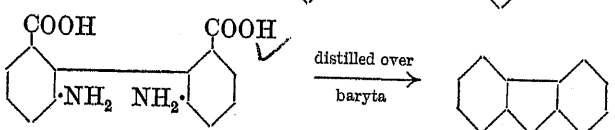
Diaminobenzidine. *Diaminocarbazole.* (87% yield.)



(From *dinitro-benzidine* or *-tolidine* by removal of $\cdot NH_2$ and reduction.) (Quantitative yield.)

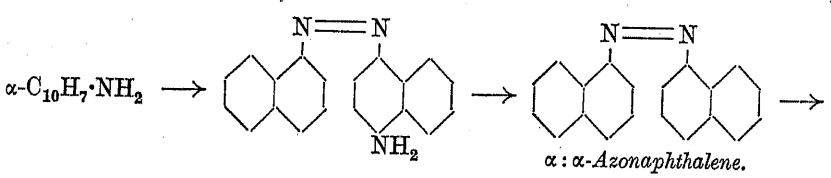
Schmidt and Kämpf [2] obtained carbazole from phenanthraquinone by the following series of reactions :



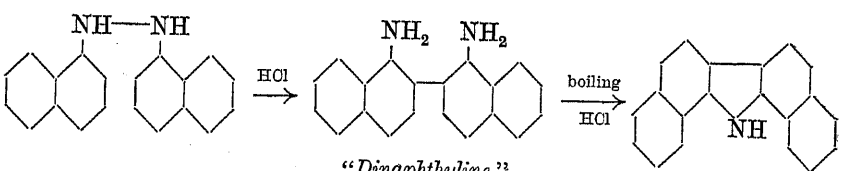


Diaminodiphenic acid. (60% yield.)

The same reaction was earlier employed by Nietzki and Goll [3] in the naphthalene series :



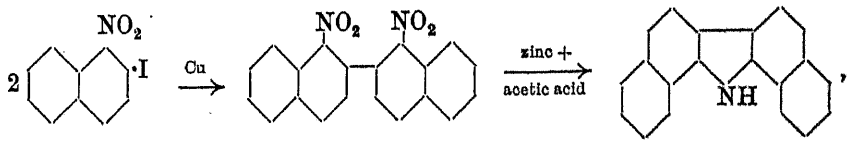
α : *α*-*Azonaphthalene.*



"Dinaphthyline."[2] *α* : *α*-*Dinaphthocarbazole.*

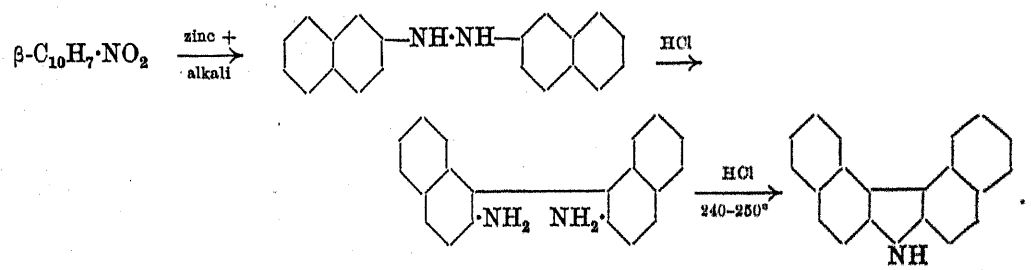
[1] Täuber, D.R.-P. 58165; *Ber.*, 1890, **23**, 3266; 1891, **24**, 197, 1033, 2597; 1892, **25**, 128.
[2] *Ibid.*, 1903, **36**, 3747. [3] *Ibid.*, 1885, **18**, 3252.

Vesely [1] obtained an identical product by the action of zinc and acetic acid upon $\alpha:\alpha'$-dinitro-$\beta:\beta'$-dinaphthyl:

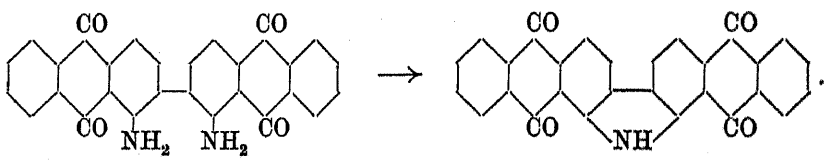


(50% yield.)

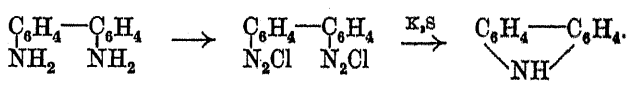
while Meisenheimer and Witte [2] prepared the isomeric dinaphthocarbazole from β-nitronaphthalene:



In the anthraquinone series a diphthaloylcarbazole has been obtained by treating $\alpha:\alpha'$-diamino-$\beta:\beta'$-dianthraquinonyl with conc. H_2SO_4 or $ZnCl_2$: [3]



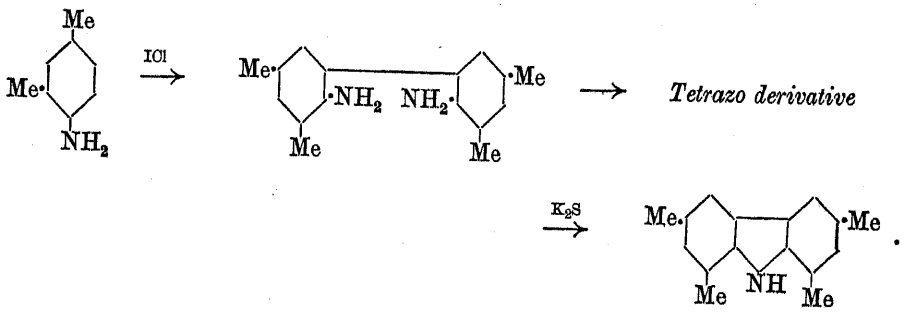
Täuber's second method for the conversion of 2:2'-diaminodiphenyl derivatives into carbazoles consists in treating the tetrazo compound with potassium sulphide.[3] This gives excellent yields and is usually more convenient than the first method:



Probably the dihydrazino derivative is intermediately produced, for $SnCl_2$ gives equal quantities of dihydrazino compound and carbazole, and when $p:p'$-diaminodiphenyl is tetrazotised and treated with K_2S $p:p'$-dihydrazinodiphenyl results. The ordinary Sandmeyer reaction with copper [4] or cuprous bromide [5] gives only small yields of carbazole. The tetrazo compound gives carbazole as main product when treated with potassium iodide solution.[6]

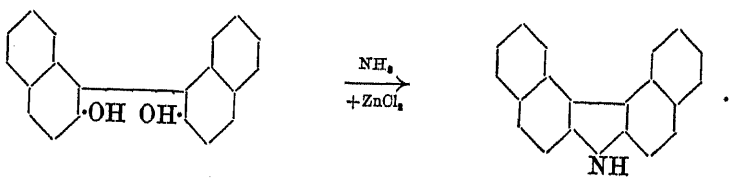
[1] *Ber.*, 1905, **38**, 136. [2] *Ibid.*, 1903, **36**, 4158. [3] D.R.-P. 267833.
[4] Täuber, *Ber.*, 1893, **26**, 1703. [5] Niementowsky, *ibid.*, 1901, **34**, 331.
[6] Dobbie, Fox and Gauge, *J. C. S.*, 1911, **99**, 1616. [7] Mascarelli, *Gazz.*, 1908, **38**, ii, 619.

Kerschbaum [1] found that diaminodixylyl, prepared in small yield by the action of ICl upon 4-*m*-xylidine, gave no carbazole by Täuber's first method, but by the second method tetramethylcarbazole was readily obtained :

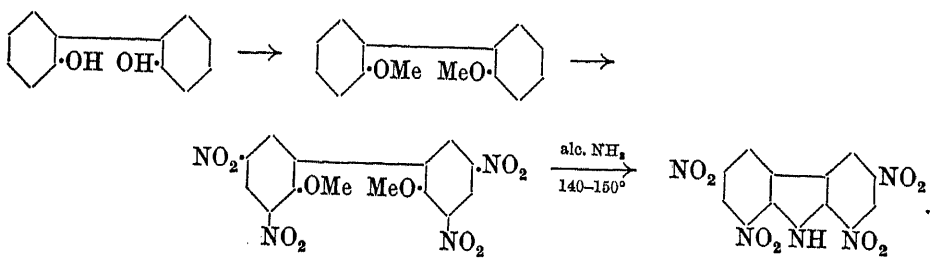


9. From 2 : 2′-dihydroxydiphenyls and ammonia : $\begin{matrix} C_6 & C_6 \\ | & | \\ X & X \end{matrix}$

Walder [2] prepared a dinaphthocarbazole by heating di-β-naphthol with zinc–chloride–ammonia at 320–330° :



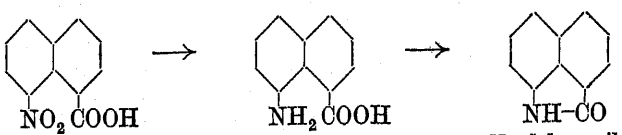
o : *o*′-Dihydroxydiphenyl, which has recently become a commercial product,* may be used for the preparation of tetranitrocarbazole.[3] It is first converted into its dimethyl ether and the methoxy groups are activated by tetranitration :



[1] *Ber.*, 1895, **28**, 2802. [2] *Ibid.*, 1882, **15**, 2173. [3] Borsche and Scholten, *ibid.*, 1917, **50**, 606.
* It is manufactured by the alkaline fusion of diphenylene oxide isolated from coal-tar.

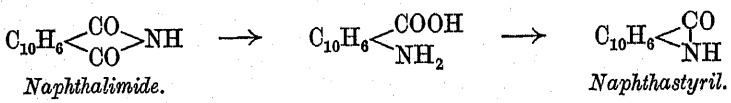
NAPHTHASTYRIL

Naphthastyril was discovered by Eckstrand,[1] who reduced 8-nitro-1-naphthoic acid and boiled the resulting amino acid with water:

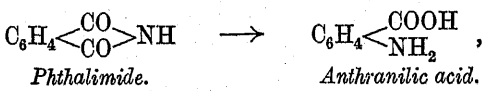


Naphthastyril.

It is best prepared from *peri*-naphthalimide. Francesconi and Rechi[2] could only obtain traces by the action of alkalies on *N*-chloronaphthalimide. By varying the conditions Ullmann and Cassirer[3] increased the yield of naphthastyril to 35%. According to Pisovschi[4] the reaction proceeds quantitatively when naphthalimide is treated with NaOCl and NaOH at 40–65°. This method, which is exactly analogous to the formation of anthranilic acid from phthalimide,



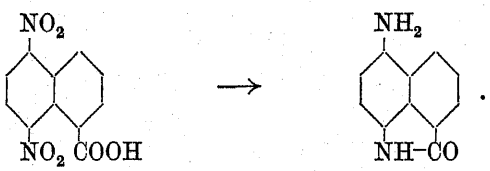
Naphthalimide. *Naphthastyril.*



Phthalimide. *Anthranilic acid.*

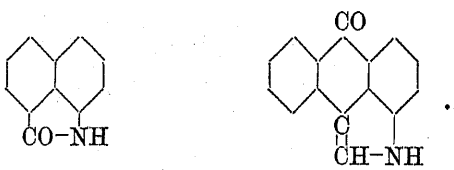
was used by Fierz and Sallmann[5] and by Dutt,[6] the yield being, however, only 50%.

An aminonaphthastyril was prepared by Eckstrand[7] by reduction and anhydrisation of dinitro-α-naphthoic acid:



PYRROLANTHRONES

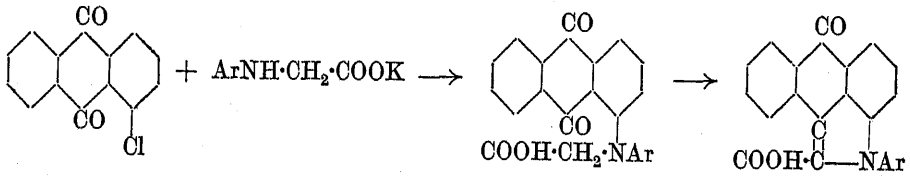
Pyrrolanthrones may be regarded as the anthracene analogues of naphthastyril:



Naphthastyril. *Pyrrolanthrone.*

[1] *Ber.*, 1885, **18**, 75; 1885, **19**, 1131; *J. pr. Chem.*, 1888, **38**, 159.
[2] *R. A. L.*, 1901, [v], **10**, ii, 85.
[3] *Ber.*, 1910, **43**, 439.
[4] *Bull.*, 1911, [iv], **9**, 86.
[5] *Helv. Chim. Acta*, 1922, **5**, 557.
[6] *J. C. S.*, 1923, **123**, 224.
[7] *Ber.*, 1887, **20**, 222.

They are obtained by condensing an α-chloroanthraquinone with a salt of phenylglycine, etc., in the presence of acetic anhydride [1] or of cuprous chloride and sodium acetate : [2]



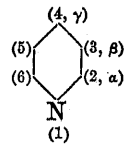
(Ar = Ph, *o*-COOH·C_6H_4·, α-$C_{10}H_7$·.)

1 : 4-Dichloro- and 1 : 4-aminochloro-anthraquinones may also be used.

[1] D.R.-P. 270789.

[2] D.R.-PP. 270790, 272613.

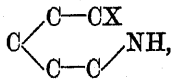
CHAPTER VII

PYRIDINES, 

Introductory :

I. Ring-closure between nitrogen and carbon atoms :

In the large majority of pyridine syntheses the ring is closed by elimination of HX from a compound of the type



where X represents NH_2, halogens or ·OH, etc.

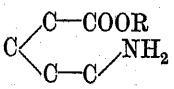
(*a*) $X = NH_2$.—In addition to the Ladenburg synthesis of *piperidine*, several other methods are based upon the intermediate formation of a 1 : 5-diamine which by elimination of ammonia or amine is converted into a *pyridine*, a *dihydropyridine* or an *α-piperidone* (sect. 1).

(*b*) $X = Halogen$.—Gabriel and his pupils have prepared a number of *piperidines* from 1 : 5-aminohalides, and the same type of ring-closure has been used for the synthesis of α- and γ-*piperidones* and of *tetrachloro-α-aminopyridine*. The condensation of 1 : 5-dihalides with ammonia or amines seems to be less suitable for the preparation of *piperidines*, doubtless owing to the numerous possible by-products (sect. 2).

(*c*) $X = OH$.—This group includes all the most important general methods.

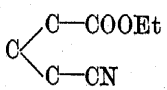
1 : 5-Amino-alcohols are converted at once into *piperidines* (sect. 3), and the ethereal oxygen in pyrane derivatives is readily replaced by ·NH· or ·NR· with production of *pyridines* from pyrylium salts or *pyridones* from pyrones (sect. 4).

Synthesis involving closure of the ring,



(R = H or alkyl),

are very numerous. δ-Amino-acids and esters yield *α-piperidones* (sect. 6), while γ-nitrile-esters of the type



are readily converted by acid hydrolysis into imides *via* the amide-acid or -ester. These nitrile-esters are obtained usually from cyanacetic ester by condensation with unsaturated esters (sect. 7) or with itself or alkylated cyanacetic esters (sect. 8). Closely related methods have been devised by Guareschi and by Thorpe (sect. 9), in which cyanacetic ester is treated with ammonia or an amine in the presence of a ketone. The Guareschi method gives excellent yields of *dicyanoglutarimides* (sect. 9). The ordinary methods for the preparation of *glutarimides*, *glutaconimides*, *camphorimides*, etc., are described in section 5.

1 : 5-Diketones react with ammonia or primary amines to give *pyridines* or *dihydropyridines* (sect. 12). In this synthesis, as in that from δ-aminoketones (sect. 13), the ring-closure is preceded by enolisation (with the exception of the example described by Haller and Ramart-Lucas, p. 215), and is thus of the δ-amino-alcohol type. γ-Keto-amides yield *α-pyridones* on anhydrisation (sect. 13).

To the same type (X = ·OH) belong the various syntheses mentioned in sections 14–25, though the final intermediate is not usually isolable in these cases.

The aldehyde-ammonia method (sect. 14) and the related methods from pyruvic acid (sect. 14), from acylpyruvic esters (sect. 15) and from acid amides and ketones (sect. 16) lead to *pyridines*. The triacetonamines (sect. 17) are *γ-pyridones*, while the condensation of diacetonamines with cyanacetic ester yields *dihydro-α-pyridones* (sect. 18). The more drastic method of Riehm (sect. 19) converts ketones into 2 : 4 : 6-trisubstituted *pyridines*. *Diketopiperidines* are formed by the addition of keto-ketens to Schiff bases (sect. 20).

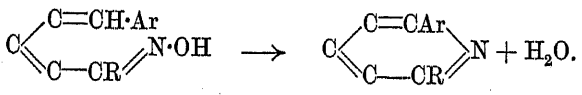
The well-known Hantzsch method (sect. 21) for *dihydropyridines* may be modified (sect. 22) so as to yield *dihydro-α-pyridones*. The Gattermann-Skita synthesis (sect. 23) gives 2 : 6-*dihydroxypyridine*-3 : 5-*dicarboxylic ester*.

β-Aminocrotonic ester (sect. 24) has been used for the synthesis of *hydroxy-* and *dihydroxypyridines*, *β-cyano-α-pyridones* and various *pyridine esters*.

A number of syntheses from "dinitriles" (acetodinitrile is the nitrile corresponding to β-aminocrotonic ester) are collected together in section 10. These lead to *α-aminopyridines*, 2 : 4-*diaminopyridines*, *α-pyridones* and *pyridines* containing alkyl or aryl groups in the 2 : 4 : 6-positions.

Oxalic ester supplies two of the pyridine carbons in Angeli's *triketopyrropiperidine* (sect. 25).

(*d*) *Other types of ring-closure between nitrogen and carbon.*—In Scholtz's synthesis (sect. 26) *pyridines* are obtained by dehydration of the oximes of δ-aryl substituted ketones :



Another synthesis from oximes is that of Wallach (sect. 27), whose "*iso*oximes" derived from *cyclo*pentanones are *α-piperidones*.

Ring-closure by addition of the ·NH_2 group at a δ-ethylene linkage (sect. 11) leads to *γ-piperidones*. A similar intramolecular addition at the ·C:N group in δ-aminonitriles or γ-amidenitriles gives *α-aminopyridines* (p. 199) or *α-aminopyridones* (pp. 205, 206), while cyano-acids yield *imides* (pp. 193, 194).

II. Ring-closure between α- and β-carbon atoms :

No simple pyridine has been built up by ring-closure in the α : β-position, but this type is exemplified in Robinson's synthesis of *tropinone* and in the preparation of an *iminazolopyridine* by an extension of a method generally used for *iso*quinolines (sect. 28).

III. Ring-closure between β- and γ-carbon atoms :

Methods of this type (sect. 29) have been used for the preparation of 2 : 4-*dihydroxypyridines*, *γ-piperidone* and 1 : 2 : 3 : 6-*tetrahydropyridines* (*e. g.* arecaidine), and in the anthraquinone series for dyestuffs of the anthrapyridone group.

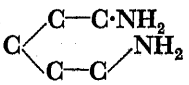
IV. Other methods:

Pyridines are formed by the widening of the pyrrole ring (sect. 30) and by the reverse process from seven- and eight-membered ring compounds (sect. 31).

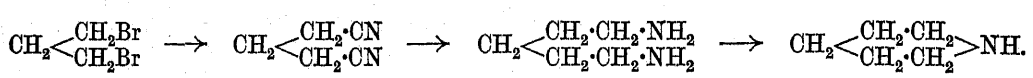
The oxidation of quinolines and other fused ring derivatives of pyridine (sect. 32) is useful for the preparation of certain *carboxylated pyridines*, especially as quinolines are frequently more easily accessible than pyridines.

The pyrogenous methods (sect. 33) are of small practical interest.

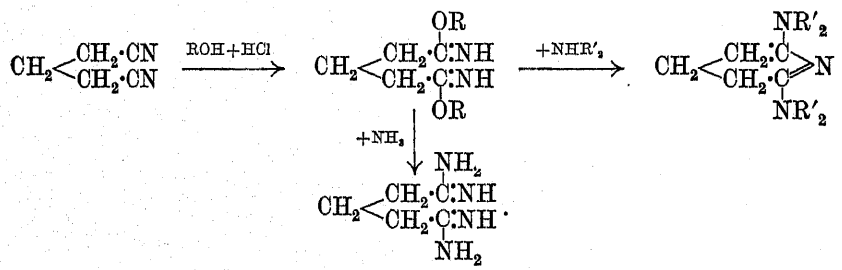
1. From 1 : 5-diamines:



The usual ring-closure by elimination of ammonia occurs when the hydrochloride of a 1 : 5-diamine is heated in HCl gas. It was by this method that Ladenburg [1] synthesised piperidine:

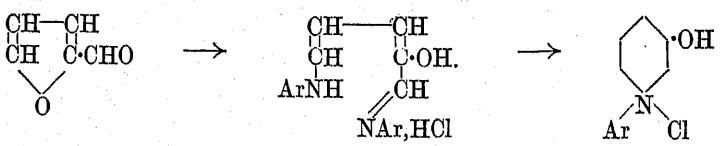


The *bis*-imino-ethers of glutaronitrile undergo a similar ring-closure when treated with an alcoholic solution of a dialkylamine,[2] though alcoholic ammonia yields only the *bis*-amidine:



(R = Me, Et, ·CH_2CHMe_2; R′ = Me, Et, Pr.)

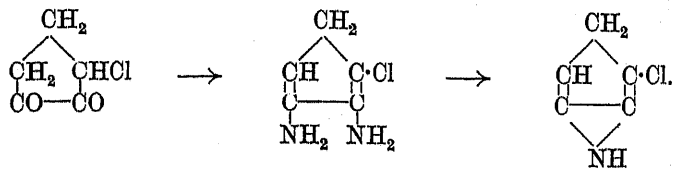
Stenhouse [3] obtained deep violet hydrochlorides of mono-acid bases by the interaction of furfural, aniline and aniline hydrochloride (or toluidine and toluidine hydrochloride). The true nature of the products was discovered independently thirty-five years later by Zincke and Mulhausen,[4] by König,[5] and by Dieckmann and Beck:[6]



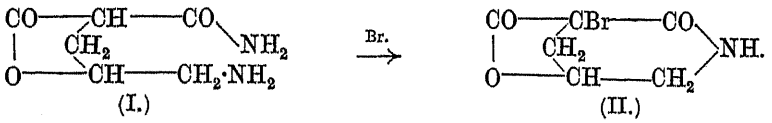
(Ar = Ph, *p*-C_7H_7, *p*-Cl·C_6H_4, *p*-EtO·C_6H_4.)

[1] *Ber.*, 1884, **17**, 388, 513; 1885, **18**, 3100; 1886, **19**, 780; *Ann.*, 1888, **247**, 52.
[2] Pinner, *Ber.*, 1890, **23**, 2945. [3] *Ann.*, 1870, **156**, 199.
[4] *Ber.*, 1905, **38**, 3824. [5] *J. pr. Chem.*, 1905, **72**, 555. [6] *Ber.*, 1905, **38**, 4122.

The curious conversion of 3-chloro-1 : 2-diketo*cyclo*pentane into 3-chloropyridine by heating with ammonium acetate [1] is probably due to the intermediate formation of a 1 : 5-diamine :

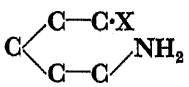


The δ-amino-amide (I) prepared by Traube, Johow and Tepohl [2] was found to undergo ring-closure when brominated either in water or acetic acid, the product being a piperidone (II) :

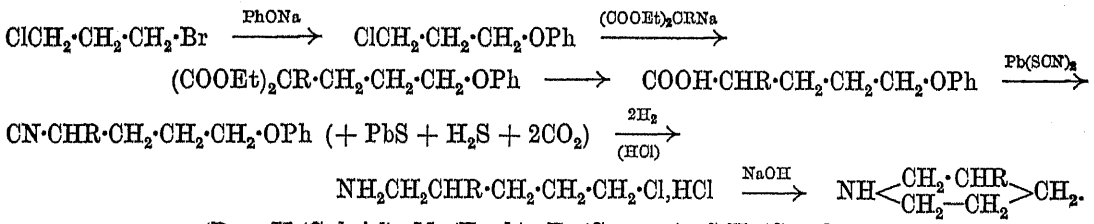


(I.) (II.)

2. From 1 : 5-aminohalides or 1 : 5-dihalides :

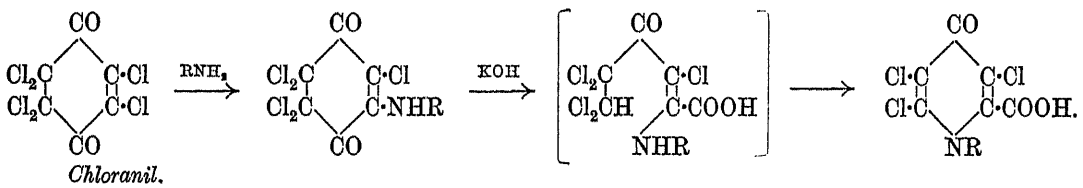


ε-Chloroamylamine is converted at once into piperidine when liberated from its salts [3] and a similar ring-closure occurs in the case of other 1 : 5-chloro-amines.[4] The method of preparation of the aminohalides is interesting :



(R = H (Gabriel), Me (Funk), Et (Granger), C_3H_7 (Günther).)

The alkaline hydrolysis of chloranil anilide leads to a pyridine derivative which is doubtless formed from an intermediate 1 : 5-aminohalogen compound.[5] The methylamide behaves similarly :

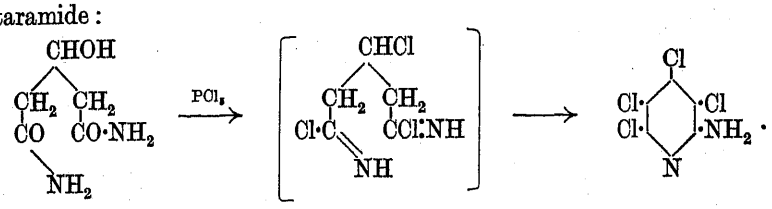


Chloranil.

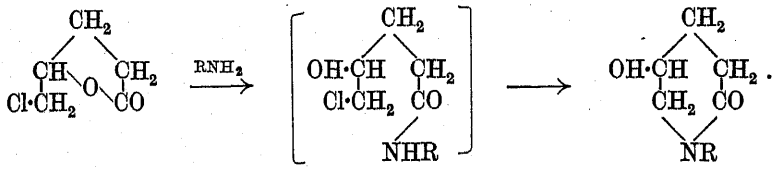
(R = Ph or Me.)

[1] Hantzsch, *Ber.*, 1889, **22**, 2827. [2] *Ibid.*, 1923, **56**, 1861. [3] Gabriel, *ibid.*, 1892, **25**, 415.
[4] Funk, *ibid.*, 1893, **26**, 2658; Granger, *ibid.*, 1895, **28**, 1197; Günther, *ibid.*, 1898, **31**, 2134.
[5] Zincke and Fuchs, *Ann.*, 1892, **267**, 6, 26, 42.

Sell and Dootson [1] obtained 2-aminotetrachloropyridine by the action of PCl_5 upon β-hydroxyglutaramide:

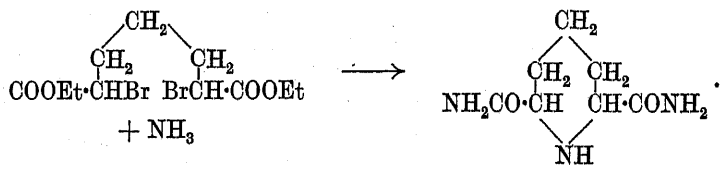


δ-Chloroamides also undergo spontaneous conversion into pyridine derivatives. Thus Leuchs and Splettstösser [2] prepared 5-hydroxy-2-piperidones by the action of ammonia or methylamine upon δ-chlorovalerolactone:



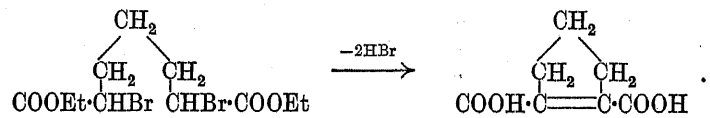
(R = H or Me.)

The action of ammonia or primary amines upon 1 : 5-dihalogenated chain compounds gives pyridine derivatives under suitable conditions. Fischer [3] obtained piperidine-2 : 6-dicarboxylic amide from dibromopimelic ester and dry liquid ammonia:

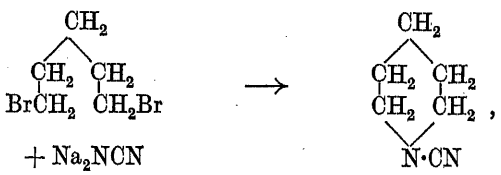


(17% yield.)

Conc. aqueous ammonia at 125° leads only to *cyclo*pentenedicarboxylic acid: [4]

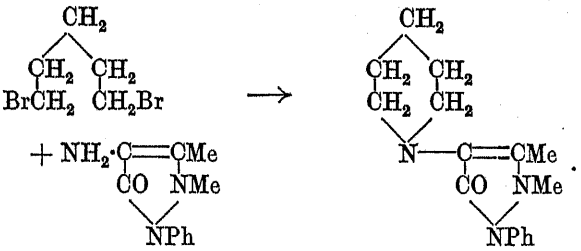


v. Braun [5] obtained only a trace of *N*-cyanopiperidine by the action of sodium cyanamide upon pentamethylene dibromide:



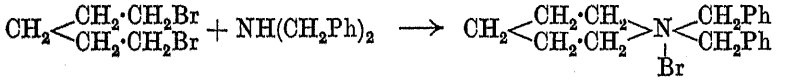
[1] *J. C. S.*, 1900, **77**, 233. [2] *Ber.*, 1907, **40**, 304. [3] *Ibid.*, 1901, **34**, 2543.
[4] Willstätter, *ibid.*, 1895, **28**, 657. [5] *Ibid.*, 1913, **46**, 1790.

but Luft [1] was more successful with 4-amino-antipyrin :

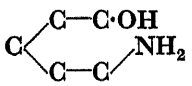


(80% yield.)

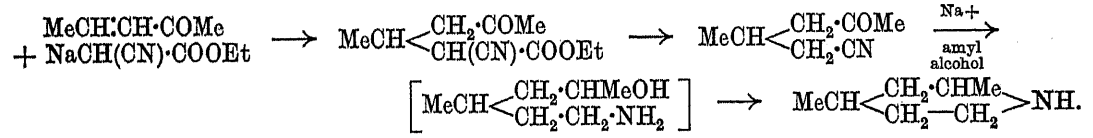
Ring-closure may even occur in the case of secondary amines : [2]



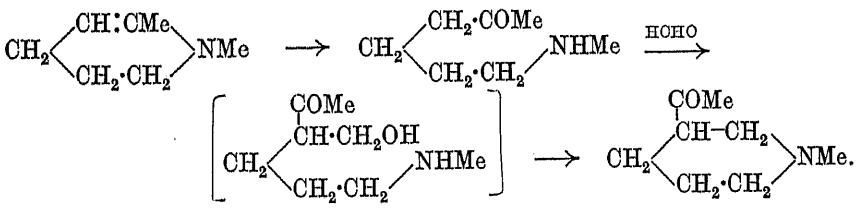
3. From 1 : 5-amino-alcohols :



Primary 1 : 5-amino-alcohols appear to be incapable of existence in the free state. The reduction of γ-aceto*iso*valeric nitrile, for example, yields 2 : 4-dimethylpiperidine : [3]



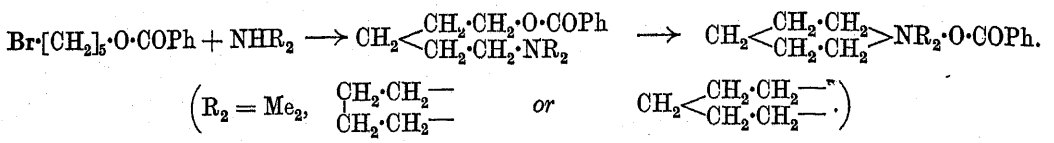
A case of ring-closure with a secondary amino-alcohol is described by Lipp and Widmann,[4] who showed that the product of the action of formaldehyde upon 1 : 6-dimethyl-1 : 2 : 3 : 4-tetrahydropyridine is 1-methyl-3-acetylpiperidine :

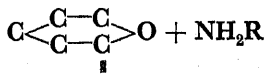


Even the tertiary amino-alcohols of this series show a strong tendency to ring-closure. v. Braun [5] prepared *O*-benzoates of the type $R_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}COPh$ by acting

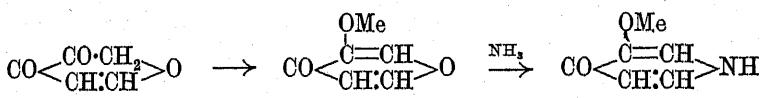
[1] *Ber.*, 1905, **38**, 4046.
[2] Scholtz and Wolfrum, *ibid.*, 1910, **43**, 2317.
[3] Wohl and Maag, *ibid.*, p. 3280.
[4] *Ann.*, 1915, **409**, 79–147.
[5] *Ber.*, 1916, **49**, 974.

upon bromoamyl benzoate with dimethylamine, pyrrolidine and piperidine. The products were converted into quaternary piperidine derivatives on distillation :

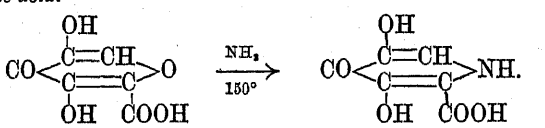


4. From pyrones, etc. : 

α- and γ-Pyrones are quite generally convertible into pyridines by the action of ammonia or primary amines. The first examples of this reaction were described by Ost,[1] though the constitution of the products was only finally determined many years later by Peratoner : [2]



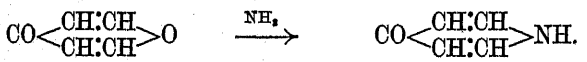
Pyromeconic acid.



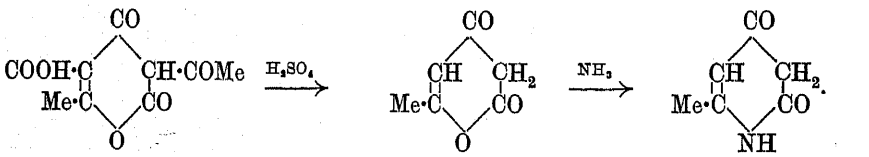
Hydroxycomenic acid. *Hydroxycomenamic acid.*

How [3] had previously converted comenic into comenamic acid, but did not realise the nature of the product.

γ-Pyridone is readily obtained by the action of ammonia upon γ-pyrone : [4]



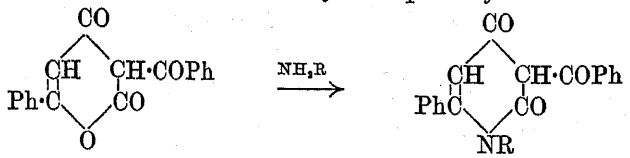
Although dehydracetic acid itself reacts abnormally with ammonia, giving lutidone (see p. 212), other related γ-pyrones yield the corresponding γ-pyridones. Thus the lactone of triacetic acid (prepared from dehydracetic acid and conc. H_2SO_4) is converted by NH_3 into 4 : 6-dihydroxy-2-methylpyridine : [5]



Dehydracetic acid. *Triacetic lactone.* *Dihydroxy-α-picoline.*

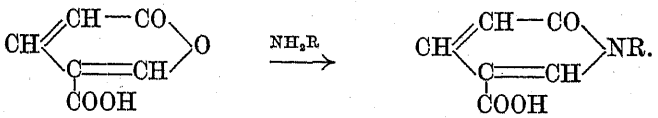
[1] *J. pr. Chem.*, 1879, **19**, 203; 1881, **23**, 441; 1883, **27**, 257; 1884, **29**, 157.
[2] *R. A. L.*, 1902, [v], **11**, i, 327; *Zentr.*, 1905, ii, 680; *Gazz.*, 1911, **41**, ii, 621, 625, 658.
[3] *Ann.*, 1851, **80**, 65. [4] Haitinger and Lieben, *Monatsh.*, 1885, **6**, 320.
[5] Collie, *J. C. S.*, 1891, **59**, 617; Collie and Myers, *ibid.*, 1892, **61**, 721.

Benzoyldehydracetic acid also reacts normally with primary amines: [1]



(R=H, Me, Et, C_3H_7·, ·$CHMe_2$, ·C_4H_9, $CHMe_2$·CH_2·, ·CMe_3, ·C_5H_{11}, $CHMe_2CH_2CH_2$·, Ph, $PhCH_2$·, $PhCH_2CH_2$·, *o*-, *m*-, *p*-C_7H_7·, PhNH·, Ph_2N·, ·OH.)

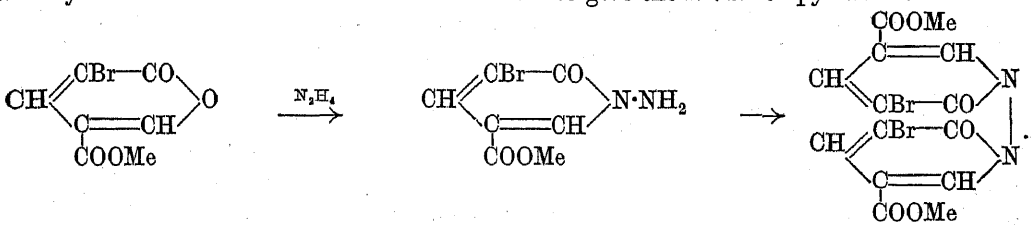
α-Pyrones in a similar manner give α-pyridones, *e. g.* coumalic acid is converted into 6-hydroxynicotinic acid by ammonia: [2]



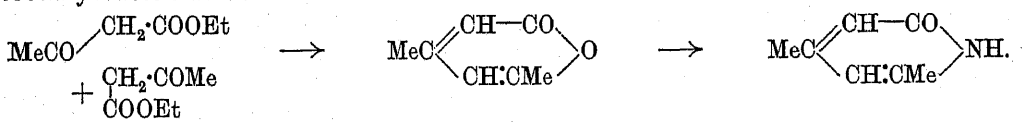
Coumalic acid.

(R=H, Me, Ph.)

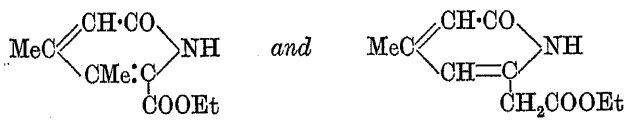
The *N*-amino-α-pyridone obtained by the action of hydrazine upon bromocoumalic methyl ester may react with a second molecule of the ester to give the *N* : *N'-bis*pyridone:



Duisberg's synthesis of ψ-lutidostyril from acetoacetic ester and ammonia [3] probably proceeds *via iso*dehydracetic acid:

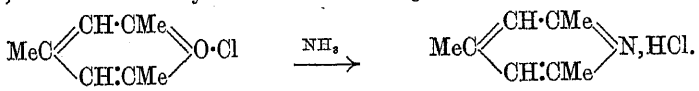


Some similar pyrone formation accounts for the conversion of β-aminocrotonic ester hydrochloride into



by dry distillation. [4]

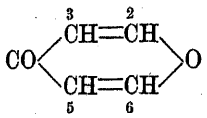
Baeyer and Piccard [5] have shown that all pyrylium salts give pyridines with ammonia—slowly in the cold, and immediately when heated. *E.g.*:



A large number of examples of this conversion have been described by Dilthey and by Gastaldi.

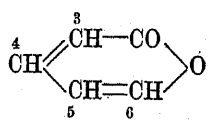
[1] Petrenko-Kritschenko and Schöttle, *Ber.*, 1911, **44**, 2826, 3648; Schöttle, *ibid.*, 1914, **47**, 688, 1547.
[2] v. Pechmann, *Ber.*, 1884, **17**, 2384, 2396; 1891, **24**, 3144; *Ann.*, 1893, **273**, 164; *Ber.*, 1904, **37**, 3829, 3837.
[3] *Ann.*, 1882, **213**, 174; Moir, *J. C. S.*, 1902, **81**, 116.
[4] Collie, *Ber.*, 1887, **20**, 445; *J. C. S.*, 1897, **71**, 299.
[5] *Ann.*, 1911, **384**, 217.

The following have been converted into pyridine derivatives by the action of ammonia, primary amines, hydroxylamine or hydrazines :

I. *γ-Pyrones :* 

	Pyrone substituents. 2	3	5	6	*Amine.*	*References.*
(γ-Pyrone)	—	—	—	—	Ammonia.	6
					Aniline.	34
(γ-Pyrone-α-carboxylic acid)	—	—	—	COOH	Ammonia.	3
					Ethylamine.	3
					Aniline.	3
					Hydroxylamine.	3
(Pyromeconic ethers)	—	—	OMe	—	Ammonia.	23
	—	—	OEt	—	Ammonia.	23
(Maltol ethers)	—	—	OMe	Me	Ammonia.	23
	—	—	OEt	Me	Ammonia.	23
(Pyro-oxymeconic)	—	—	OH	OH	Aniline.	26
(Comenic acid derivatives)	—	OH	—	COOH	Ammonia.	1, 3
	—	OEt	—	COOH	Ammonia.	26
	—	OEt	—	COOEt	Hydroxylamine.	26
(Chelidonic acid)	COOH	—	—	COOH	Aniline.	31, 34
					Toluidines.	31
					4-*m*-Xylidine.	31
					α-Naphthylamine.	31
(Triacetlactone)	Me	—	—	OH	Ammonia.	13, 14
	Me	—	Me	Me	Ammonia.	32
(Benzoyldehydracetic)	Ph	—	COPh	OH	Ammonia, alkylamines, etc.*	28
	Me	COOEt	COOEt	Me	Ammonia.	8
					Methylamine.	8
					Aniline.	8

(Dehydracetic acid with ammonia gives lutidone. 5, 7, 16, 17, 21)

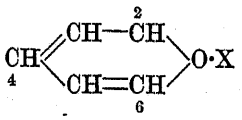
II. *α-Pyrones :* 

	Pyrone substituents. 3	4	5	6	*Amine.*	*References.*
(Coumalic acid derivatives)	—	—	COOH	—	Ammonia.	4
					Methylamine.	4
					Aniline.	15
	—	—	COOMe	—	Aniline.	4, 15
	—	—	COOEt	—	Methylamine.	30
	Cl	—	COOMe	—	Ammonia.	22
	Br	—	COOMe	—	Ammonia.	4
					Aniline.	4
					Hydrazine.	22
					1-Aminotriazole.	25

* See p. 189.

	Pyrone substituents.				Amine.	References.
	3	4	5	6		
	—	Me	—	Me	Ammonia.	2
	—	Ph	—	Ph	Ammonia.	38
	—	Me	—	·CH_2COOEt	Ammonia.	9, 18
	COOEt	—	COOEt	Me	Ammonia	24
					Aniline.	24
	COOEt	—	COOEt	·OEt	Ammonia.	12
	—	Me	Me	COOEt	Ammonia.	9, 18
(*iso*Dehydracetic)	—	Me	COOH	Me	Ammonia.	11
(Citracoumalic)	—	·CH_2COOH	·COOH	·CH_2COOH*	Ammonia.	11
	COOEt	Ph	—	Ph	Ammonia.	38
	COOMe	$PhCH_2$·	—	*p*-ClC_6H_4·	Ammonia.	39

III. *Pyrylium Salts:*



Substituents.			Amine.	References.
2	4	6		
Me	Me	Me	Ammonia.	27
			Methylamine.	27
			p-Toluidine.	27
Me	Ph	Me	Ammonia.	27
			p-Toluidine.	27
Me	Ph	Ph	Ammonia.	40
Ph	Me	Ph	Phenylhydrazine.	33
Ph	Ph	Ph	Ammonia.	35
			Phenylhydrazine.	33
Ph	Ph	*p*-ClC_6H_4	Ammonia.	35
Ph	Ph	*p*-BrC_6H_4	Ammonia.	35
Ph	Ph	*p*-C_7H_7	Ammonia.	29, 35
Ph	Ph	*p*-MeO·C_6H_4	Ammonia.	29
Ph	Ph	*p*-Ph·C_6H_4	Ammonia.	29
Ph	Ph	β-$C_{10}H_7$	Ammonia.	29
Ph	Ph	3 : 4-$(MeO)_2C_6H_3$·	Ammonia.	37
Ph	*p*-MeO·C_6H_4	Ph	Ammonia.	29
Ph	*p*-OH·C_6H_4	Ph	Aniline.	36
p-ClC_6H_4	Ph	*p*-ClC_6H_4	Ammonia.	29
p-BrC_6H_4	Ph	*p*-BrC_6H_4	Ammonia.	37
Ph	*p*-C_7H_7	*p*-C_7H_7	Ammonia.	35
p-ClC_6H_4	*p*-C_7C_7	*p*-C_7H_7	Ammonia.	35
p-C_7H_7	Ph	*p*-C_7H_7	Ammonia.	29
p-C_7H_7	*p*-C_7H_7	*p*-C_7H_7	Ammonia.	35
Ph	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	Ammonia.	29
p-MeO·C_6H_4	Ph	*p*-MeO·C_6H_4	Ammonia.	29
p-MeO·C_6H_4	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	Ammonia.	29
Me	*p*-MeO·C_6H_4	*p*-MeO·C_6H_4	Phenylhydrazine.	41

References.

[1] How, *Ann.*, 1851, **80**, 65. [2] Duisberg, *ibid.*, 1882, **213**, 174. [3] Ost, *J. pr. Chem.*, 1883, **27**, 257; 1884, **29**, 57, 378. [4] v. Pechmann, *Ber.*, 1884, **17**, 2391, 2398. [5] Haitinger, *Monatsh.*, 1885, **6**, 105. [6] Haitinger and Lieben, *ibid.*, p. 320. [7] Haitinger, *Ber.*, 1885, **18**, 452. [8] Conrad and Guthzeit, *ibid.*,

* Loses CO_2 during reaction.

1886, **19**, 24; 1887, **20**, 154. [9] Collie, *Ber.*, 1887, **20**, 445. [10] Feist, *Ann.*, 1890, **257**, 264. [11] Nieme and v. Pechmann, *ibid.*, 1891, **261**, 203, 206. [12] Guthzeit and Dressel, *ibid.*, 1891, **262**, 89; *Ber.*, 1893, **26**, 2795. [13] Collie, *J. C. S.*, 1891, **59**, 617. [14] Collie and Myers, *ibid.*, 1892, **61**, 721. [15] v. Pechmann, *Ann.*, 1893, **273**, 179. [16] v. Pechmann and Neger, *ibid.*, p. 207. [17] Sedgwick and Collie, *J. C. S.*, 1895, **67**, 399. [18] Collie, *ibid.*, 1897, **71**, 299. [19] Moir, *ibid.*, 1902, **81**, 116. [20] Peratoner, *R. A. L.*, 1902, [v], **11**, i, 327. [21] Michaelis and Hölken, *Ann.*, 1904, **331**, 254. [22] v. Pechmann and Mills, *Ber.*, 1904, **37**, 3832, 3837. [23] Peratoner and Tamburello, *Zentr.*, 1905, ii, 680. [24] Simonsen, *J. C. S.*, 1908, **93**, 1022. [45] Bülow and Weber, *Ber.*, 1909, **42**, 1994. [26] Peratoner, *Gazz.*, 1911, **41**, ii, 621, 625, 658. [27] Baeyer and Piccard, *Ann.*, 1911, **384**, 217. [28] Petrenko-Kritschenko and Schöttle, *Ber.*, 1911, **44**, 2826, 3648; Schöttle, *ibid.*, 1914, **47**, 688, 1547. [29] Dilthey, *J. pr. Chem.*, 1921, **102**, 209–240. [30] Ruzicka, *Helv. Chim. Acta*, 1921, **4**, 504. [31] Smirnoff, *ibid.*, p. 599. [32] Philippi and Seka, *Ber.*, 1921, **54**, 1089. [33] Schneider and Seebach, *ibid.*, p. 2296. [34] Borsche and Bonacker, *ibid.*, p. 2678. [35] Gastaldi, *Gazz.*, 1921, **51**, ii, 299–306. [36] Dilthey, *Ber.*, 1922, **55**, 59. [37] *Idem*, *Ann.*, 1922, **428**, 33. [38] Kohler, *J. A. C. S.*, 1922, **44**, 379. [39] Kohler and Smith, *ibid.*, p. 631. [40] Gastaldi, *Gazz.*, 1922, **52**, i, 173, 305. [41] *Idem*, *R. A. L.*, 1922, [v], **31**, i, 257. [42] Dilthey, *J. pr. Chem.*, 1922, **104**, 28–36. [43] Gastaldi and Pyretti, *Gazz.*, 1923, **53**, i, 11–15.

5. From γ-dicarboxylic derivatives : $C<^{C—COOH}_{C—COOH} + NH_2R$

The imides of the glutaric and glutaconic series are readily obtained by the usual methods. Thus ammonium glutarate when heated at 150–250° gives glutarimide : [1]

$$CH_2<^{CH_2\cdot COONH_4}_{CH_2\cdot COONH_4} \longrightarrow CH_2<^{CH_2\cdot CO}_{CH_2\cdot CO}>NH.$$

The substituted glutaconic acids obtained from cyanacetic esters by Rogerson and Thorpe [2] were similarly converted into glutaconimides by distillation of their ammonium salts :

$$MeC<^{CR\cdot COONH_4}_{CHR\cdot COONH_4} \longrightarrow MeC<^{CR—CO}_{CHR\cdot CO}>NH.$$

(R = H, Me, Et; R′ = H, Me, Et.)

A convenient method in many cases is to pass dry NH_3 into the molten anhydride of the acid, allowing the water to distil off as formed. Winzer [3] prepared camphorimide in this way :

$$CH_2—CH(CMe_2)—CO>O \xrightarrow{NH_3} CH_2—CH(CMe_2)—CO>NH.$$
$$CH_2—CMe—CO \qquad\qquad CH_2—CMe—CO$$

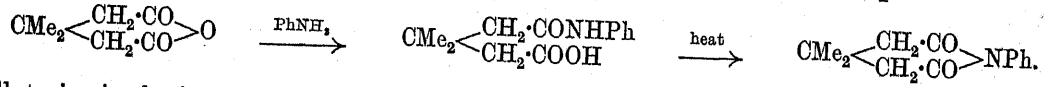
The esters of γ-dicarboxylic acids are converted into imides by treatment with ammonia. *E. g.* Ruhemann [4] prepared several glutaconimides by this method :

$$CH<^{CH\cdot COOEt}_{CHR\cdot COOEt} \xrightarrow{NH_3} CH<^{CH—CO}_{CHR\cdot CO}>NH.$$

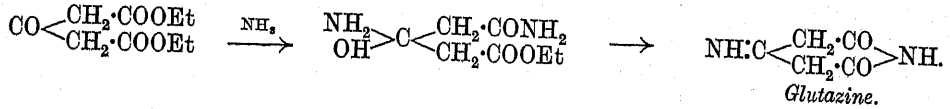
(R = Me, Et, $PhCH_2$.)

[1] Bernheimer, *Gazz.*, 1882, **12**, 281.
[2] *J. C. S.*, 1905, **87**, 1685–1713.
[3] *Ann.*, 1890, **257**, 309.
[4] *J. C. S.*, 1893, **64**, 259, 874; *Ber.*, 1894, **27**, 1272.

γ-Amide-acids or -esters readily yield imides when heated, this method being especially suitable for the preparation of *N*-substituted imides such as the glutaranils. For example : [1]

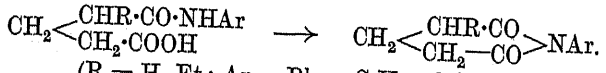


Glutazine is obtained by heating with Na_2CO_3 the amide-ester resulting from the action of ammonia upon acetonedicarboxylic ester : [2]



Glutazine.

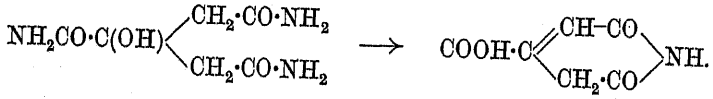
Auwers [3] prepared a series of glutarimides by the action of heat or acetyl chloride upon glutaranilic acids :



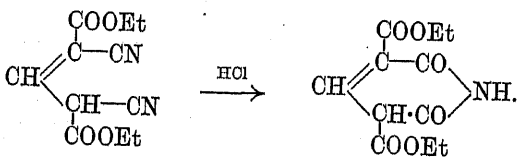
(R = H, Et; Ar = Ph, *p*-C_7H_7·, β-$C_{10}H_7$·.)

Where R = Me only bimolecular anils were obtained.[4]

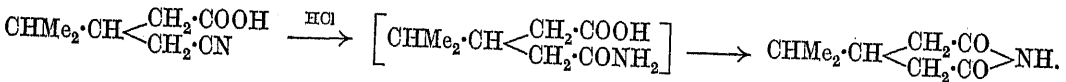
Citramide, heated with conc. H_2SO_4, is converted into citrazinic acid : [5]



The conversion of glutaronitrile into glutarimide [6] by dilute H_2SO_4 at 180–200° probably involves the intermediate formation of the diamide. Ruhemann and Browning [7] heated α : γ-dicyanoglutaconic ester with HCl and obtained dicarbethoxyglutaconimide :



γ-Cyano-acids are similarly transformed into imides *via* the amide-acid. Thus : [8]

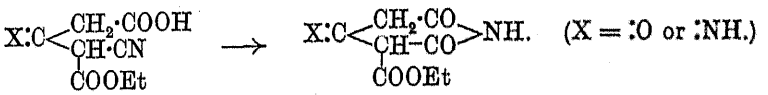


Other examples of this type are mentioned under the Guareschi and Thorpe methods (p. 201).

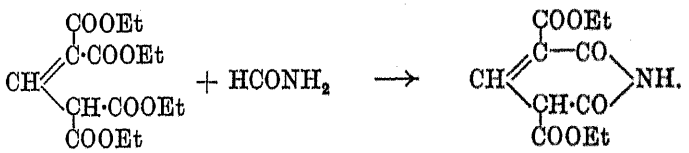
γ-Cyano-acids may also be converted directly into imides by a reaction precisely analogous to the formation of secondary amides from acids and nitriles. Thus Baron, Remfry and Thorpe [9]

[1] Perkin, *J. C. S.*, 1896, **69**, 1476.
[2] Stokes and v. Pechmann, *Ber.*, 1886, **19**, 2694; v. Pechmann, *ibid.*, 1887, **20**, 2655.
[3] *Ann.*, 1896, **292**, 196–215.
[4] *Ibid.*, p. 209.
[5] Behrmann and Hofmann, *Ber.*, 1884, **17**, 2681; Ruhemann, *ibid.*, 1887, **20**, 799.
[6] Bogert and Eccles, *J. A. C. S.*, 1902, **24**, 20.
[7] *J. C. S.*, 1898, **73**, 284.
[8] Howles and Thorpe, *Proc. C. S.*, 1899, **15**, 104.
[9] *J. C. S.*, 1904, **85**, 1756.

obtained glutazine-3-carboxylic ester and the corresponding triketo-compound by heating the appropriate cyano-acid at about 150° for ten minutes :



In certain cases it is an advantage to use ammonia in a less volatile form. Guareschi [1] obtained camphorimide by heating camphoric acid with urea at 125°, thiourea at 170° or ammonium thiocyanate at 200°. Similarly, Ruhemann and Sedgwick [2] used formamide for the conversion of dicarboxyglutaconic ester into its imide (ammonia breaks down the ester into malonic ester and aminomethylenemalonic ester) :



These various methods have been applied to the preparation of the following imides :

a = from ammonium salts.
b = from acid anhydrides and ammonia or amines, with or without isolation of the amide-acid.
c = from esters and ammonia, or from amide-esters.
d = from diamides, nitriles or nitrile-acids.

Imide.	*References.* *a.*	*b.*	*c.*	*d.*
Glutarimide.	5	13	—	31
Glutaranil.	—	13, 21	—	—
α-Ethylglutaranil.	—	21	—	—
α-Ethylglutar-*p*-tolil.	—	21	—	—
α-Ethylglutar-α-naphthil.	—	21	—	—
α-*iso*Propylglutaranil.	—	22	—	—
β-*iso*Propylglutaranil.	—	—	—	27
β-Phenylglutarimide.	—	26	—	—
Glutazine.	—	—	8, 10	—
Glutazine-3-carboxylic ester.	—	—	—	34A
α : α-Dimethylglutarimide.	—	28	—	—
α : α-Dimethylglutaranil.	—	24, 30	—	—
α : α′-Dimethylglutarimide.	20	—	—	—
α : α′-Dimethylglutaranil.	—	19	—	—
α : α′-Dimethylglutar-*p*-tolil.	—	19, 21	—	—
α : α-Dimethylglutar-α-naphthil.	—	19	—	—
α : α-Dimethylglutar-β-naphthil.	—	19	—	—
α : β-Dimethylglutarimide.	—	33	—	—
α-Cyano-β-methylglutarimide.	—	—	45	—
α-Cyano-β : γ-dimethylglutarimide.	—	—	45	—
Glutarimide-β-acetamide.	—	—	44	—
α : α′-Dimethylglutar-*p*-tolil.	—	21	—	—
β : β-Dimethylglutarimide.	—	41	—	—
β : β-Dimethylglutaranil.	—	22, 33	—	—
α : α : α′-Trimethylglutarimide.	—	—	—	36
Camphorimide.	1, 29, 39	1, 4, 11, 12, 17, 23, 32, 34	—	—
Camphormethylimide.	—	14	—	—
Camphorethylimide.	6	—	—	—
Camphorbenzylimide.	—	14	—	—

[1] *Bull.*, 1888, [ii], **49**, 299.

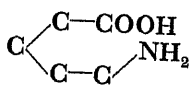
[2] *Ber.*, 1895, **28**, 825.

Imide.	*References.*			
Aminocamphorimide.	—	3	—	—
*iso*Fenchocamphorimide.	43	—	—	—
Glutaconimide.	—	—	—	—
*α-Methylglutaconimide.	—	—	—	—
*β-Methylglutaconanil.	—	—	—	2
β-Methylglutaconimide.	—	38	15, 16	—
β-Methylglutaconanil.	35	—	—	—
β-Methylglutacon-*p*-toli.	—	37	—	—
*α-Ethylglutaconimide.	—	37	—	—
β-Phenylglutaconanil.	—	—	—	—
β-Phenylglutacon-*p*-tolil.	—	38	15	—
Citrazinic acid.	—	38	—	—
*α : β-Dimethylglutaconimide.	—	—	—	—
*α : β-Dimethylglutaconanil.	35	—	—	7, 9
*α : γ-Dimethylglutaconanil.	—	40	—	—
*α-Ethyl-β-methylglutaconimide.	—	40	—	—
*α-Ethyl-β-methylglutaconanil.	35	—	—	—
α-Methyl-γ-ethylglutaconanil.	—	42	—	—
*α-Benzyl-β-methylglutaconanil.	40	—	—	—
α : γ-Dicarbethoxyglutaconimide.	—	42	—	—
α : α : β-Trimethylglutaconanil.	—	—	—	—
α : β : γ-Trimethylglutaconimide.	—	25	18	25A
α : β : γ-Trimethylglutaconanil.	35	—	—	—
	—	40	—	—

* The α- and γ-positions in glutaconimides are equivalent except where the α-carbon carries two substituent groups.

References.

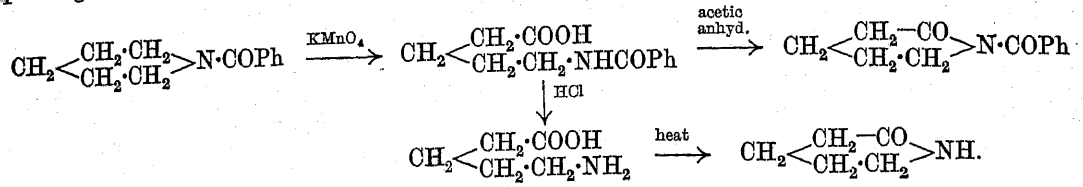
[1] Laurent, *Ann.*, 1846, **60**, 329. [2] Kekulé (see Ruhemann, *J. C. S.*, 1893, **73**, 351). [3] Wreden, *Ann.*, 1872, **163**, 339. [4] Ballo, *ibid.*, 1879, **197**, 331. [5] Bernheimer, *Gazz.*, 1882, **12**, 281. [6] Wallach and Kamenski, *Ann.*, 1882, **214**, 247. [7] Berhmann and Hofmann, *Ber.*, 1884, **17**, 2681. [8] Stokes and v. Pechmann, *ibid.*, 1886, **19**, 2694. [9] Ruhemann, *ibid.*, 1887, **20**, 799. [10] v. Pechmann, *ibid.*, p. 2655. [11] Guareschi, *Bull.*, 1888, [ii], **49**, 299. [12] Winzer, *Ann.*, 1890, **257**, 309. [13] Bödtker, *Dissn. Leipzic*, 1891. [14] Hoogewerf and van Dorp, *Rec. trav. chim.*, 1893, **12**, 12—22. [15] Ruhemann, *J. C. S.*, 1893, **63**, 259, 874. [16] *Idem*, *Ber.*, 1894, **27**, 1272. [17] Noyes, *Amer. Chem. J.*, 1894, **16**, 502. [18] Ruhemann and Sedgwick, *Ber.*, 1895, **28**, 825. [19] Auwers, Oswald and Thorpe, *Ann.*, 1895, **285**, 237. [20] Auwers and Thorpe, *ibid.*, p. 339. [21] Auwers, *ibid.*, 1896, **292**, 196–215. [22] Perkin, *J. C. S.*, 1896, **69**, 1476, 1497. [23] Oddo and Leonardi, *Gazz.*, 1896, **26**, i, 405, 423. [24] Tiemann, *Ber.*, 1897, **30**, 255. [25] Perkin and Thorpe, *J. C. S.*, 1897, **71**, 1186, 1189. [25A] Ruhemann and Browning, *ibid.*, 1898, **73**, 284. [26] Herrmann and Vorländer, *Zentr.*, 1899, i, 730. [27] Howles and Thorpe, *Proc. C. S.*, 1899, **15**, 104. [28] Blaise, *Bull.*, 1899, [iii], **21**, 628. [29] Tafel and Eckstein, *Ber.*, 1901, **34**, 3277. [30] Blaise, *Compt. rend.*, 1902, **134**, 1113. [31] Bogert and Eccles, *J. A. C. S.*, 1902, **24**, 20. [32] Noyes and Warren, *Amer. Chem. J.*, 1902, **28**, 480. [33] Blaise, *Bull.*, 1903, [iii], **29**, 333, 1028, 1034. [34] Bredt, *Ann.*, 1903, **328**, 343. [34A] Baron, Remfry and Thorpe, *J. C. S.*, 1904, **85**, 1746. [35] Rogerson and Thorpe, *ibid.*, 1905, **87**, 1686–1713. [36] Blaise and Courtot, *Bull.*, 1906, [iii], **35**, 580. [37] Fichter and Schwab, *Ann.*, 1906, **348**, 255. [38] Feist and Pomme, *ibid.*, 1909, **370**, 71, 78, 79. [39] Evans, *J. C. S.*, 1910, **97**, 2237. [40] Thole and Thorpe, *ibid.*, 1911, **99**, 2187, 2237. [41] Komppa, *Zentr.*, 1912, i, 1472. [42] Bland and Thorpe, *J. C. S.*, 1912, **101**, 1570, 1747. [43] Sandelin, *Ann.*, 1913, **396**, 305, 313, 318. [44] Ingold and Nickolls, *J. C. S.*, 1922, **121**, 1644. [45] Hope and Sheldon, *ibid.*, p. 2227.

6. From δ-amino-acids or esters: 

δ-Amino-acids show less tendency to ring-closure than might perhaps be expected. Their acyl derivatives are quite stable (*cf.* v. Braun's fission of benzoylpiperidine). Schotten [1] prepared

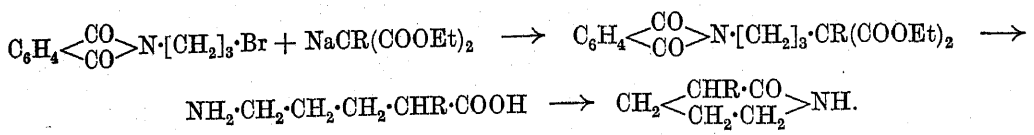
[1] *Ber.*, 1888, **21**, 2235.

δ-aminovaleric acid from benzoylpiperidine by oxidation and hydrolysis. The free base yields piperidone when heated; its benzoyl derivative is only converted into benzoylpiperidone by prolonged heating with acetic anhydride:

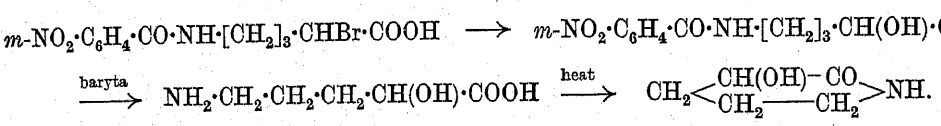


Benzenesulphonylpiperidine gives similar results.[1]

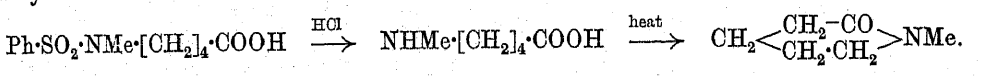
δ-Aminovaleric acid was also prepared by Gabriel [2] by the phthalimide method, and its ethyl, propyl and benzyl homologues by Aschan.[3] The amino-acids are converted into piperidones by distillation:



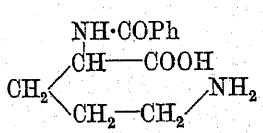
Lipp and Widmann [4] employed a similar method, using acetoacetic ester in place of malonic ester. Piperidones have also been prepared from δ-amino-acids by Fischer and Zemplen [5] and by Fischer and Bergmann: [6]



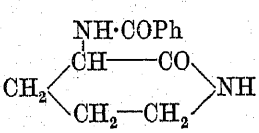
Similarly:



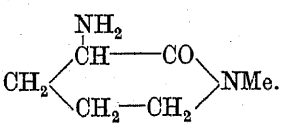
α-Benzoylornithine (I) is usually accompanied by the corresponding lactam (II): [7]



(I.)



(II.)

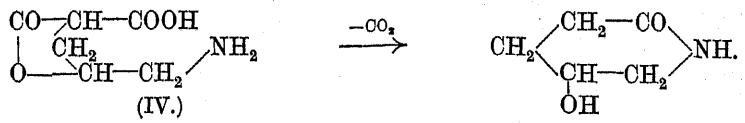


(III.)

δ-Toluenesulphonyl-α-benzoyl-ornithine is also partially converted into lactam during the preparation. δ-Methyl-ornithine gives 1-methyl-3-amino-2-piperidone (III) when warmed.

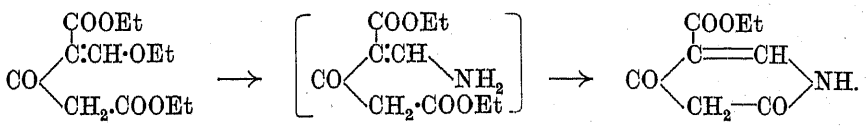
[1] Schotten and Schlömann, *Ber.*, 1891, **24**, 3687. [2] *Ibid.*, 1890, **23**, 1769.
[3] *Ibid.*, p. 3632; 1891, **24**, 2443. [4] *Ann.*, 1915, **409**, 143.
[5] *Ber.*, 1909, **42**, 4878. [6] *Ann.*, 1913, **398**, 110–114.
[7] Thomas, Kapfhammer and Flaschenträger, *Z. physiol. Chem.*, 1922, **124**, 75.

Traube, Johow and Tepohl [1] observed the formation of 5-hydroxy-2-piperidone when the amino-lactone (IV) was heated, carbon dioxide being lost:

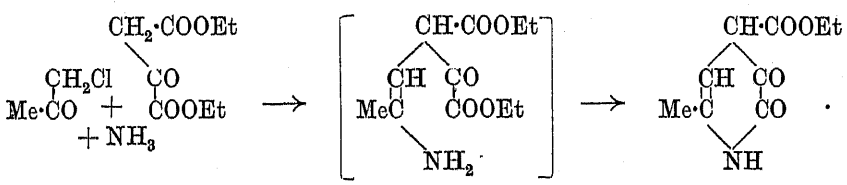


(IV.)

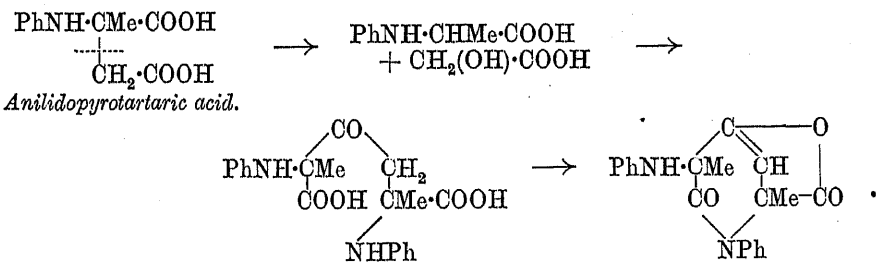
The ethoxymethylene-acetonedicarboxylic ester obtained by Errera [2] is converted by the action of ammonia into a dihydroxypyridine derivative. As the second ester group is unattacked, the reaction probably proceeds *via* the amino-ester rather than *via* the amide:



Feist [3] extended to oxalacetic ester the Hantzsch pyrrole synthesis from chloroacetone, acetoacetic ester and ammonia. Very little of the expected pyrrole derivative is formed, the main product being 6(or 5)-methyl-2 : 3-diketotetrahydro*iso*nicotinic ester:



When "anilidopyrotartaric acid" is heated it yields, in addition to citraconanil, a pyridine derivative, the formation of which is explained as follows by Reissert: [4]



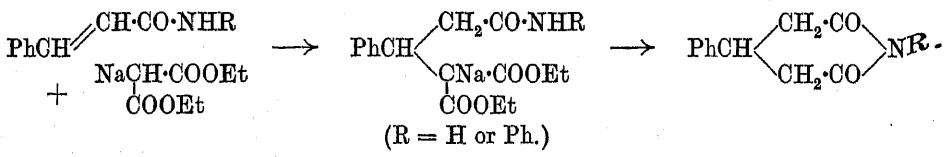
Anilidopyrotartaric acid.

7.-From condensation products of cyanacetic or malonic ester with unsaturated esters etc.: $C<^{C-COOEt}_{C-CONH_2}$

In this and the two following sections are grouped certain methods by which glutarimides and glutaconimides may be synthesised from cyanacetic or malonic ester.

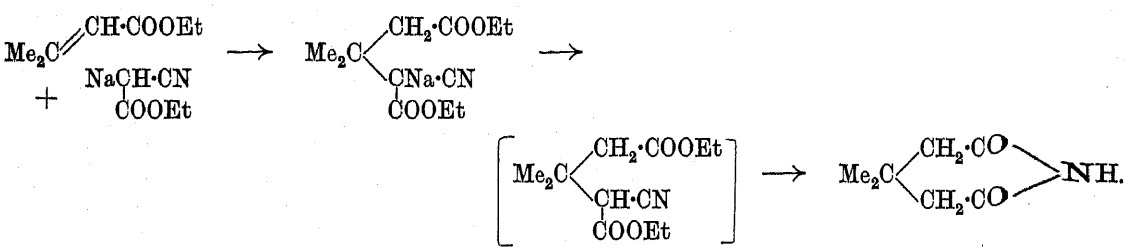
[1] *Ber.*, 1923, **56**, 1861.
[2] *Ibid.*, 1898, **31**, 1682.
[3] *Ibid.*, 1902, **35**, 1537, 1545.
[4] *Ibid.*, 1888, **21**, 1362, 1380, 1385; 1890, **23**, 542.

Hermann and Vorländer [1] observed that sodio-malonic ester forms additive products with the amides of cinnamic acid, PhCH:CH·CONHR, and that ring-closure follows at once in certain cases with the production of a β-phenylglutarimide :

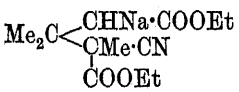


(R = H or Ph.)

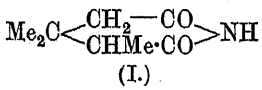
Cyanacetic ester is more reactive than malonic ester in this respect. Perkin and Thorpe [2] condensed sodiocyanacetic ester with β : β-dimethylacrylic ester and obtained glutarimides by hydrolysis of the product with HCl or alcoholic KOH :



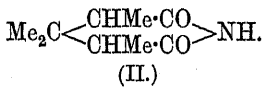
When sodio-methylcyanacetic ester is used, the sodio-derivative first formed is



which may be hydrolysed to trimethylglutarimide (I) [3] or may be methylated before hydrolysis, in which case the product is tetramethylglutarimide (II) : [4]

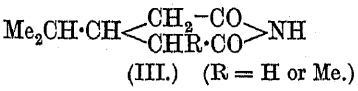


(I.)

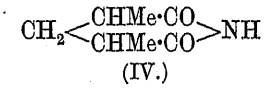


(II.)

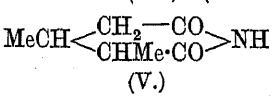
The reaction has been extended to other unsaturated esters, the resulting glutarimides being (III),[5] IV,[6] V [7] and VI : [8]



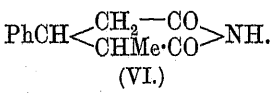
(III.) (R = H or Me.)



(IV.)



(V.)



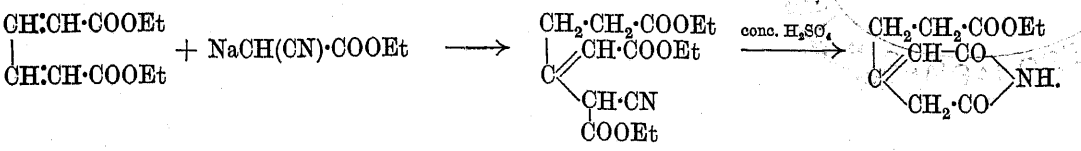
(VI.)

Tiglic and angelic esters, MeCH:CMe·COOEt, also condense readily with cyanacetic ester.[9]

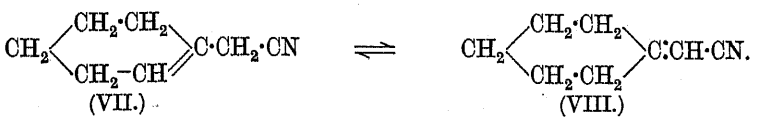
[1] *Zentr.*, 1899, i, 730. [2] *J. C. S.*, 1899, **75**, 53. [3] Perkin and Thorpe, *ibid.*, p. 64.
[4] Thorpe and Young, *ibid.*, 1900, **77**, 939. [5] Howles, Thorpe and Udall, *ibid.*, p. 943.
[6] *Idem*, *ibid.*, p. 949. [7] Thorpe and Young, *ibid.*, 1903, **83**, 356.
[8] Carter and Lawrence, *Proc. C. S.*, 1900, **16**, 178. [9] Blaise, *Bull.*, 1903, [iii], **29**, 332.

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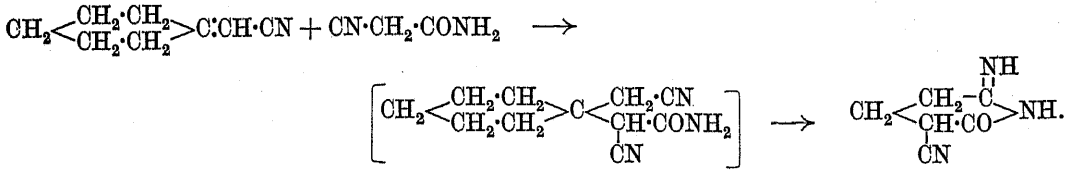
An interesting case has recently been investigated by Farmer : [1]



*cyclo*Hexenylacetonitrile is a tautomeric compound :

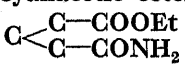


With cyanacetamide it reacts in the semicyclic form (VIII), giving an additive product which at once undergoes ring-closure, forming the iminopiperidone : [2]

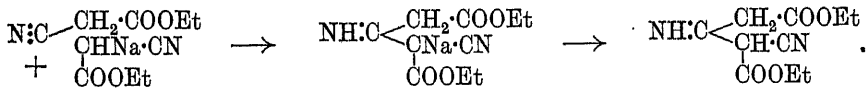


Exactly similar behaviour is observed with *cyclo*pentenylacetonitrile.[3]

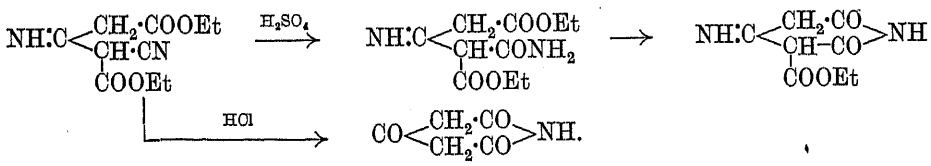
8. From condensation products of cyanacetic esters with sodiocyanacetic ester etc. :



Thorpe has shown that cyanacetic ester condenses with its sodio-derivative to give an imino-cyano-glutaric ester :

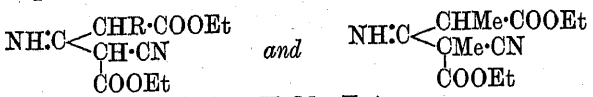


Similar condensations occur with alkylated cyanacetic esters.* The products are converted by cold conc. H_2SO_4 into glutarimides and by hot conc. HCl into trihydroxypyridines :



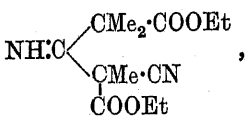
[1] *J. C. S.*, 1922, **121**, 2015. [2] Birch and Kon, *ibid.*, 1923, **123**, 2444.
[3] Cf. also Thorpe's synthesis, p. 203.
* The intermediate sodio-compound may also be alkylated in the usual way.

Baron, Remfry and Thorpe [1] in this way obtained pyridine derivatives from



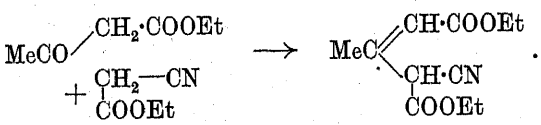
(R = H, Me, Et.)

The trimethylated compound,

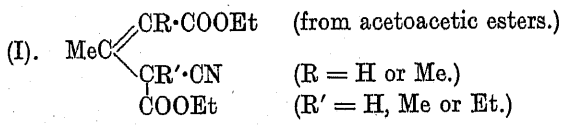


failed to undergo ring-closure.

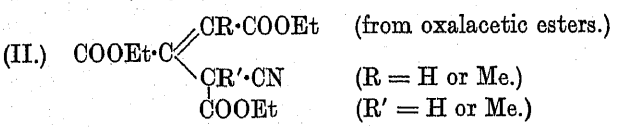
The reaction was extended by Rogerson and Thorpe [2] to the condensation products of cyanacetic ester with acetoacetic and oxalacetic esters and their alkyl derivatives :



The nitrile esters used were of the following types :



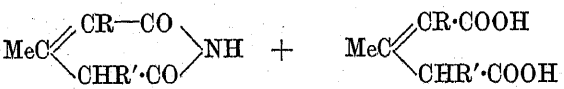
(α-*Cyanoglutaconic.*)



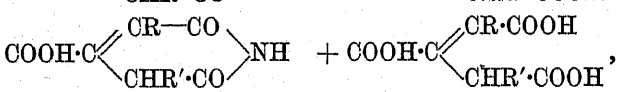
(α-*Cyano-aconitic.*)

In both cases, conc. H_2SO_4 brought about ring-closure, provided the α-position was not alkylated (*i.e.* R′ must be hydrogen). Hot conc. HCl usually gave a mixture of imide and acid :

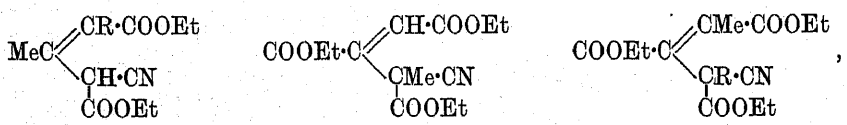
From I



From II



but in five cases, viz. :

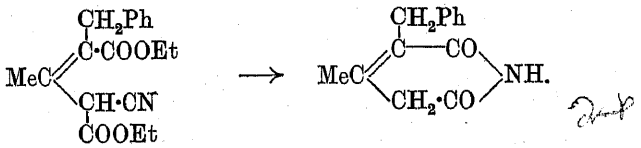


no imide was formed. Alcoholic KOH converted all the nitrile-esters into imides.

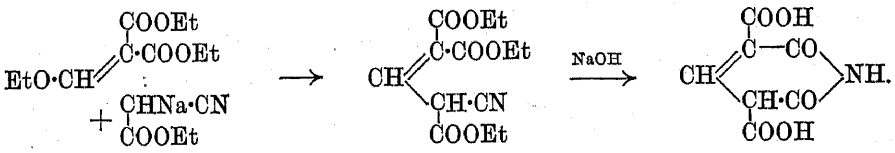
[1] *J. C. S.*, 1904, **85**, 1740, 1749, 1753, 1758.

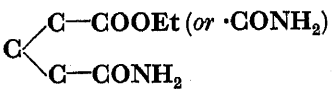
[2] *Ibid.*, 1905, **87**, 1685; 1906, **89**, 631.

Bland and Thorpe [1] obtained β-methyl-γ-benzylglutaconimide by the action of conc. HCl or alcoholic KOH upon benzylated α-cyano-β-methylglutaconic ester:

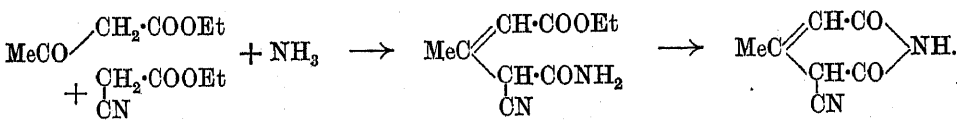


The condensation product from cyanacetic ester and ethoxymethylenemalonic ester was converted into dicarboxyglutaconimide by Errera: [2]

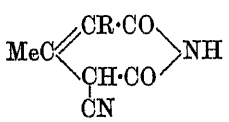


9. The Guareschi and Thorpe syntheses: 

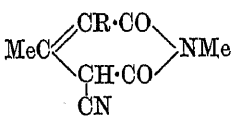
The Guareschi pyridine syntheses are of two types. In the first, cyanacetic ester is condensed with acetoacetic ester in the presence of ammonia and gives a glutaconimide: [3]



Instead of ammonia and the two esters, a mixture of acetoacetamide and cyanacetic ester or of acetoacetic ester and cyanacetamide may be used. The reaction has been extended to alkylated esters and primary amines, and Guareschi has in this way prepared:

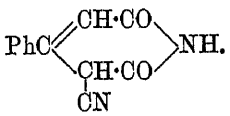


(R = H, Me, Et, C_3H_7, ·$CHMe_2$, C_4H_9, ·CH_2CHMe_2, ·$CH_2CH_2CHMe_2$, ·CH_2·$CH{:}CH_2$, OH·CH_2CH_2·, $PhCH_2$·, ·CH_2COOEt.)



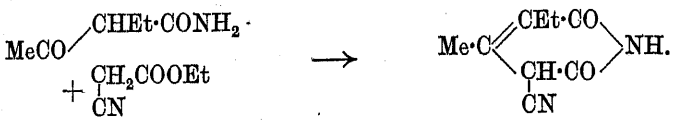
(R = H, Me.)

and



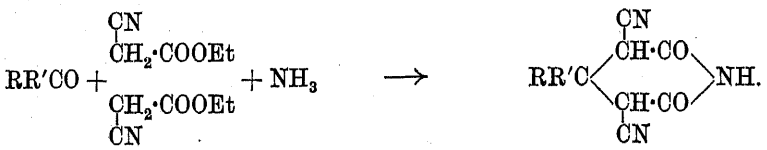
[1] *J. C. S.*, 1912, **101**, 1743. [2] *Ber.*, 1898, **31**, 1243.
[3] Guareschi, *J. C. S.*, Abstr. 1897, i, 168; *Zentr.*, 1896, i, 601; 1905, ii, 681.

Guareschi and Sabbatani [1] similarly condensed cyanacetic ester with propionylpropionic ester and ammonia or methylamine. The method is fully described by Ruzicka and Fornasir,[2] who obtained an 85% yield of α-cyano-β-methyl-γ-ethylglutaconimide from ethylacetoacetamide and cyanacetic ester:

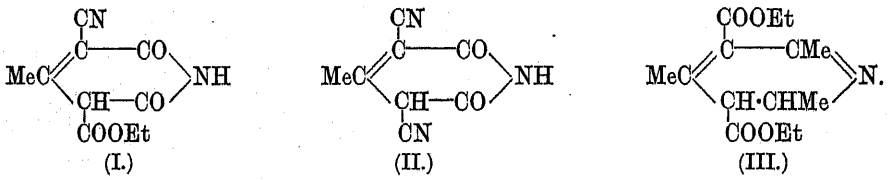


Malonic ester cannot replace cyanacetic ester in these reactions.

In the second type of Guareschi synthesis, a mixture of cyanacetic ester and a ketone (or, less suitably, an aldehyde) is treated with alcoholic ammonia. The product gives a dicyanoglutarimide on acidification:



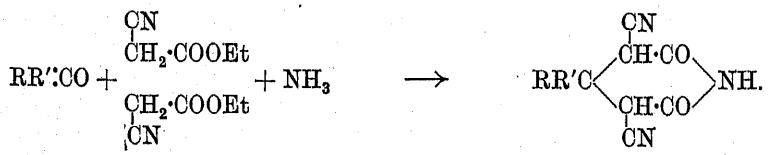
The method originated in Guareschi's observation [3] that when a mixture of cyanacetic ester and ethylidene-acetoacetic ester is treated with ammonia, there is obtained, instead of the expected cyano-ester-imide (I), a dicyano-imide (II), together with a little dihydrocollidine-dicarboxylic ester (III):



The formation of compounds II and III must have been preceded by hydrolysis of the ethylidene derivative. The acetaldehyde so formed condenses with cyanacetic ester (or its amide) under the influence of the ammonia present,[4] and the resulting glutaric ester (or amide) is converted into the imide. The small amount of collidine derivative is formed by the ordinary Hantzsch reaction (see p. 227) from some of the acetoacetic ester.

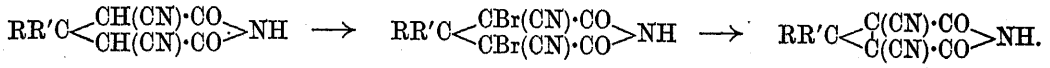
Similar products resulted from benzaldehyde, cyanacetic ester, acetoacetic ester and ammonia.

Much better results are obtained, however, when ketones are used in place of aldehydes, and a variety of β:β-disubstituted α:α′-dicyanoglutarimides has been prepared (see list at end of this section):

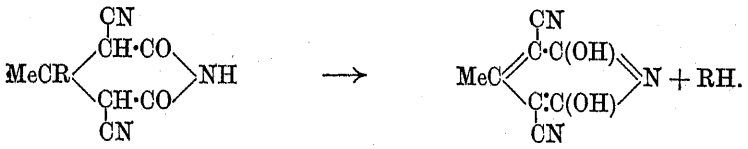


[1] *Zentr.*, 1897, i, 904.
[2] *Helv. Chim. Acta*, 1919, **2**, 343.
[3] *Zentr.*, 1897, i, 927, 928; Quenda, *ibid.*, i, 903.
[4] Cf. Knoevenagel, *Ber.*, 1902, **35**, 2392, footnote.

These products have special properties which make them useful in synthesis. They may be hydrolysed to $\beta:\beta$-dialkylglutaric acids.[1] They are easily brominated in the two α-positions, and the dibromo-compounds as readily lose their halogen on boiling with formic or acetic acid, yielding *cyclo*propane derivatives :[2]

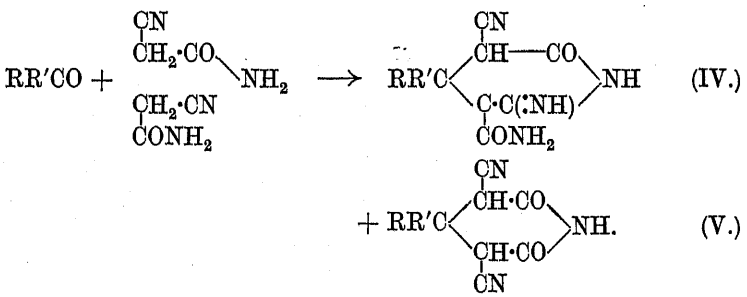


A curious property of the dicyanoglutarimides is their tendency to pass into dihydroxypyridines by loss of RH,[3] which recalls Riehm's syntheses (pp. 225, 263) :

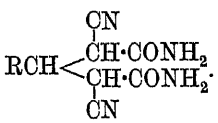


This reaction is, in fact, a convenient method for the preparation of pure ethane, propane, butane and hexane. Ammonia is passed into a mixture of cyanacetic ester and the appropriate ketone, R·CO·Me, and the gas evolved is collected over water or dilute acid.

In the Thorpe synthesis cyanacetamide is used in place of cyanacetic ester and a trace of piperidine catalyses the reaction. The main product, however, is an imino-imide (IV), only 10% or less of the dicyano-imide (V) being obtained :[4]



The reaction was further investigated by Thorpe and Wood[5] and by Day and Thorpe,[6] who found that when aldehydes were used in place of ketones the amount of dicyano-amide (V) was still further reduced, the yield of imino-compound (IV) was very small and the main product was a dicyano-diamide :



[1] Kon, *J. C. S.*, 1921, **119**, 818.

[2] Guareschi and Grande, *Zentr.*, 1899, ii, 439; Minozzi, *Gazz.*, 1900, **30**, i, 265; Ghiglieno, *Zentr.*, 1910, ii, 806, 807; Guareschi, *Gazz.*, 1918, **48**, ii, 83; Birch, Gough and Kon, *J. C. S.*, 1921, **119**, 1320; Deshapande and Thorpe, *ibid.*, 1922, **121**, 1438.

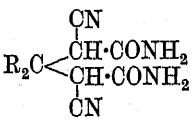
[3] Guareschi, *Zentr.*, 1897, i, 927; Pasquali, *ibid.*, i, 903, 904; Grande, *ibid.*, p. 903; Guareschi and Grande, *ibid.*, 1898, ii, 544.

[4] Thole and Thorpe, *J. C. S.*, 1911, **99**, 422.

[5] *Ibid.*, 1913, **103**, 1586.

[6] *Ibid.*, 1920, **117**, 1465.

The yields in both the Guareschi and the Thorpe syntheses depend upon the nature of the ketone, R·CO·R′. If R and R′ are primary or secondary groups, both methods are satisfactory. If one group is tertiary, the Guareschi yield is reduced and the Thorpe method fails. With two tertiary groups, both methods fail. From these results it appears that the two methods are, contrary to Thorpe's suggestion,[1] quite distinct. The Thorpe method leads to *cis*- and *trans*-diamides,

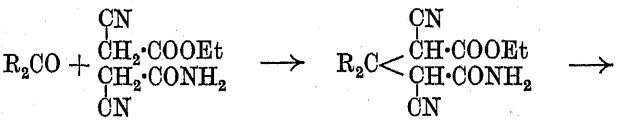


cis.

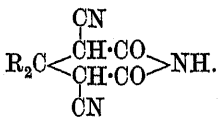


trans.

which give respectively the dicyanoimide (V) and the iminoimide (IV). In the Guareschi method, on the other hand, cyanacetamide is formed, and condenses (as in the earlier Guareschi synthesis from cyanacetamide and keto-esters) with cyanacetic *ester* and the ketone to give first an amide ester (VI) which at once undergoes ring-closure to the imide (V):



(VI.)



The Guareschi and Thorpe methods have been applied to the following aldehydes and ketones:

Aldehyde or Ketone.	*References.* *Guareschi method.*	*Thorpe, method.*
Me·CHO	1	13
Et·CHO	—	13
C_3H_7·CHO	—	13
Ph·CHO	1	13
Me·COMe	1, 2, 5, 14, 15, 19	7
Et·COMe	1, 3, 4, 5	7
C_3H_7·COMe	1, 2, 6	—
$CHMe_2$·COMe	6, 10	—
C_4H_9·COMe	1, 2	—
EtCHMe,COMe	10	—
C_5H_{13}·COMe	1, 2, 5, 18	—
$PhCH_2$·COMe	9, 10, 18	—
$PhCH_2CH_2$·COMe	9	—
$PhCH_2CHMe$·COMe	10	—
Et·CO·Et	14, 16, 18, 19	—
$PhCH_2$·CO·Et	9, 10	—
$PhCH_2CH_2$·CO·Et	9	—

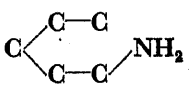
[1] Kon and Thorpe, *J. C. S.*, 1919, **115**, 686.

Aldehyde or Ketone.	*References. Guareschi method.*	*Thorpe. method.*
$PhCH_2 \cdot CO \cdot C_3H_7$	9	—
$PhCH_2 \cdot CO \cdot CHMe_2$	10	—
$PhCH_2 \cdot CO \cdot CH_2CHMe_2$	9	—
*cyclo*Pentanone.	10, 14, 18	11
2-Methyl*cyclo*pentanone.	10	—
*cyclo*Hexanone.	14, 15, 17	7
2-Methyl*cyclo*hexanone.	10	—
3-Methyl*cyclo*hexanone.	18	8, 10
4-Methyl*cyclo*hexanone.	18	8, 10
2 : 4-Dimethyl*cyclo*hexanone.	10	—
Dihydrocarvone.	10	—
Suberone.	12, 14	—

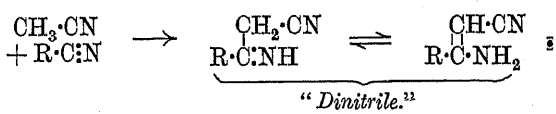
References.

[1] Guareschi, *Zentr.*, 1897, i, 927–928. [2] Pasquali, *ibid.*, pp. 903–904. [3] Grande, *ibid.*, p. 903. [4] Guareschi and Grande, *ibid.*, 1898, ii, 544. [5] *Idem*, *ibid.*, 1899, ii, 439, 440. [6] Minozzi, *Gazz.*, 1900, **30**, i, 265. [7] Thole and Thorpe, *J. C. S.*, 1911, **99**, 430. [8] Thorpe and Wood, *ibid.*, 1913, **103**, 1592. [9] Guareschi, *Gazz.*, 1918, **48**, ii, 83. [10] Kon and Thorpe, *J. C. S.*, 1919, **115**, 686. [11] *Idem*, *ibid.*, pp. 697, 701. [12] Day, Kon and Stevenson, *ibid.*, 1920, **117**, 639. [13] Day and Thorpe, *ibid.*, p. 1469. [14] Kon, *ibid.*, 1921, **119**, 818. [15] Birch, Gough and Kon, *ibid.*, p. 1320. [16] Deshapande and Thorpe, *ibid.*, 1922, **121**, 1435. [17] Kon and Thorpe, *ibid.*, p. 1802. [18] Birch and Thorpe, *ibid.*, pp. 1825–1836. [19] Birch and Kon, *ibid.*, 1923, **123**, 2447.

10. From "dinitriles":

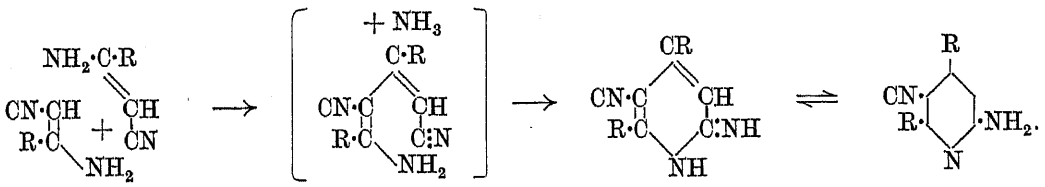


Acetonitrile condenses with itself or with other nitriles in the presence of sodium or sodium ethoxide to form bimolecular additive products:



The properties and reactions of the "dinitriles" so prepared have been investigated by Holtzwart and especially by E. v. Meyer.

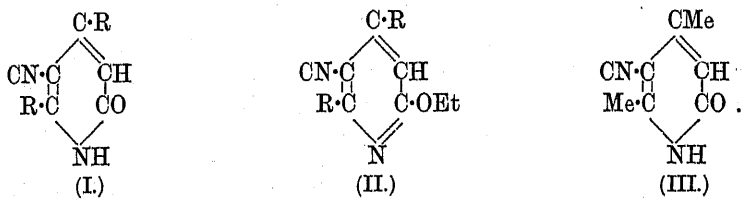
v. Meyer[1] heated acetodinitrile with $ZnCl_2$, HCl or $C_2H_4Br_2$ and obtained a pyridine derivative. Similar products resulted from benzo- and *p*-toluo-acetodinitriles:[2]



(R = Me, Ph, *p*-C_7H_7.)

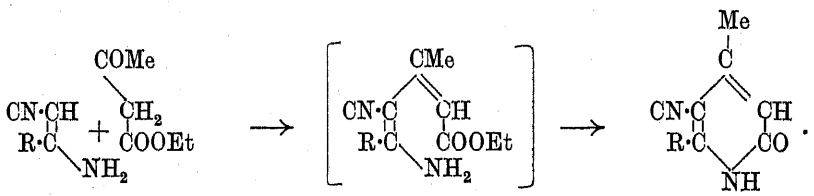
[1] *Zentr.*, 1908, ii, 591. [2] v. Meyer, *J. pr. Chem.*, 1914, **90**, 1–52.

The condensation is brought about, not only by the reagents mentioned, but also by anhydrous organic acids (cyanacetic, succinic, malic, glycollic or hydroxy*iso*butyric) at 140°. If the condensing agent is not carefully dried, hydrolysis of the imino group occurs and the product is a pyridone (I). In the presence of alcohol an ethoxypyridine (II) results :



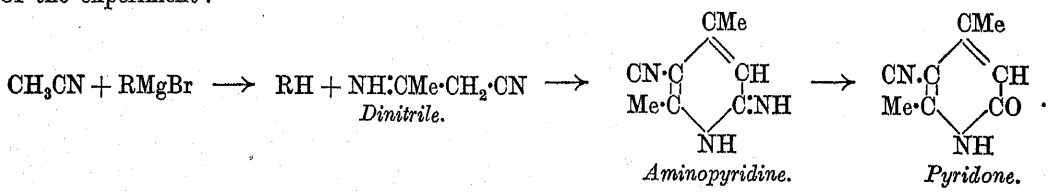
(I.) (II.) (III.)

This explains the formation of 5-cyano-4 : 6-dimethyl-α-pyridone (III) by the action of hot water upon acetodinitrile.[1] Pyridones of type I are also produced by a very similar reaction when acetodinitrile or benzoacetonitrile is condensed with acetoacetic ester : [2]



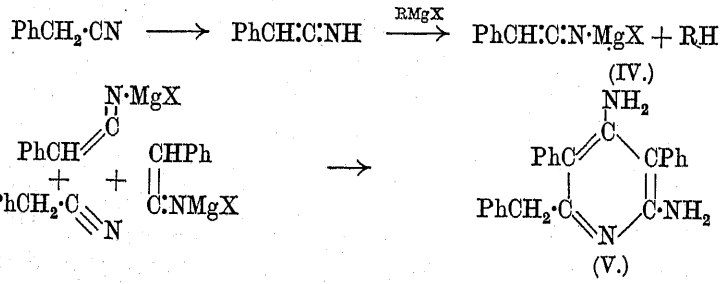
(R = Me, Ph.)

Bruylants,[3] in studying the action of Grignard reagents upon acetonitrile, observed the formation of acetodinitrile, the aminopyridine or the pyridone, according to the conditions of the experiment :



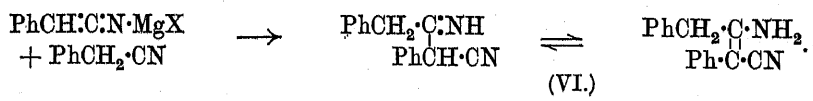
Dinitrile. *Aminopyridine.* *Pyridone.*

The later work of Rondou [4] suggests a different interpretation of the reaction. Benzyl cyanide when treated with Grignard reagents gives first a compound (IV) which may combine with more nitrile to form a diaminopyridine (V) or the dinitrile (VI). The dinitrile is not considered to be the source of the pyridine derivative :



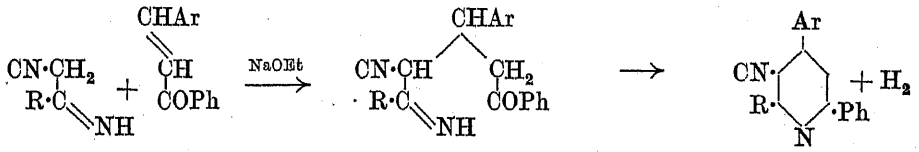
(IV.) (V.)

[1] Holtzwart, *J. pr. Chem.*, 1889, **39**, 329; Moir, *J. C. S.*, 1902, **81**, 100. [2] v. Meyer, *loc. cit.*
[3] *Bull. Acad. roy. Belg.*, 1922, [v], **8**, 7. [4] *Zentr.*, 1923, i, 87.



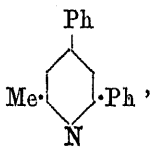
No pyridine derivative is obtained in this way from propionitrile, EtCN.[1]

A second method for the preparation of pyridines from dinitriles was also devised by v. Meyer.[2] The dinitrile is condensed with an arylidene-acetophenone in the presence of NaOEt :

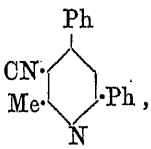


(R = Me, Ph or p-C_7H_7.
Ar = Ph, p-$MeOC_6H_4$·, 3 : 4-$CH_2<O>C_6H_3$· or PhCH:CH.)

Styryl p-tolyl ketone, PhCH:CH·CO·C_7H_7, behaves similarly with acetodinitrile. The reaction fails with benzalacetone, benzalcamphor and benzalpyrazolone. Gastaldi [3] has thrown considerable doubt upon the constitution of these products. He prepared 2 : 4-diphenyl-6-methylpyridine,

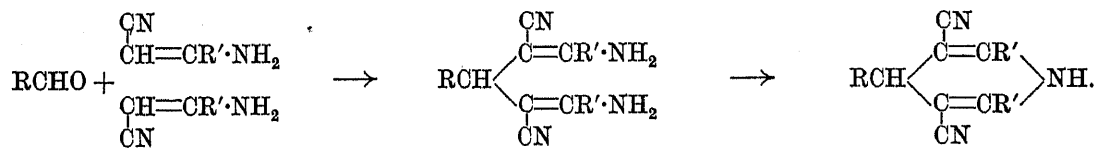


from the corresponding pyrylium salt (see p. 191), and found it to be different from the product obtained by v. Meyer by hydrolysis of



followed by removal of CO_2.

In E. v. Meyer's general method for the preparation of dicyanodihydropyridines from dinitriles and aldehydes [4] a 1 : 5-diamine is obtained as an intermediate product : [5]



Dinitrile.

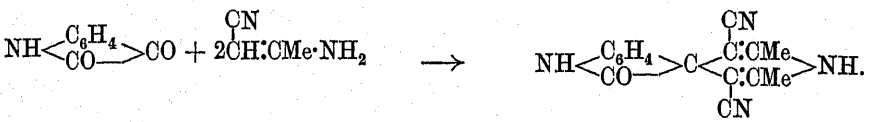
Mohr condensed acetodinitrile (R′ = Me) with benzaldehyde, anisaldehyde, m-nitrobenzaldehyde,

[1] Baerts, *Zentr.*, 1923, i, 86.
[2] *Ibid.*, 1908, ii, 591; *J. pr. Chem.*, 1908, **78**, 497.
[3] *Gazz.*, 1922, **52**, i, 169, 305.
[4] *Zentr.*, 1908, ii, 591; *J. pr. Chem.*, 1908, **78**, 507; 1915, **92**, 175.
[5] Mohr, *ibid.*, 1897, **56**, 124.

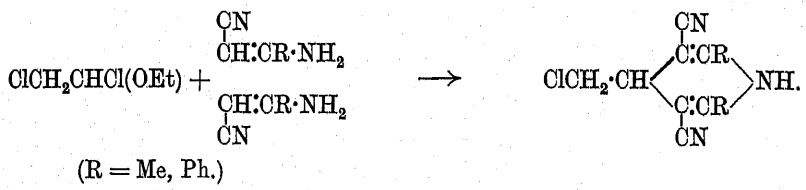
piperonal and cinnamaldehyde. With salicylaldehyde the yield was small, and the reaction failed with phenylacetaldehyde.

v. Meyer in addition used formaldehyde and acetaldehyde and extended the reaction to benzoacetodinitrile (R′ = Ph), which he condensed with formaldehyde, acetaldehyde, benzaldehyde and *o*-nitrobenzaldehyde.

The ketonic (*i.e.* the β-) ·CO· group in isatin (but not in sodium isatate—see p. 291) also reacts in this way with acetodinitrile : [1]

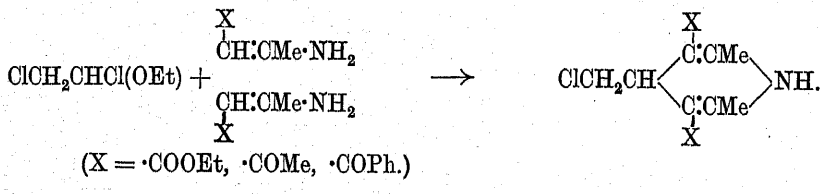


Benary and Löwenthal [2] used α : β-dichloroethyl ether, $ClCH_2·CHCl·OEt$ (which in many of its reactions behaves as $ClCH_2·CHO$) in place of the aldehyde :



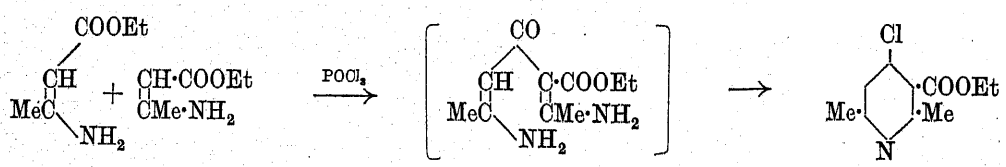
(R = Me, Ph.)

Compounds of the β-aminocrotonic ester type may replace the dinitrile. Thus Benary [3] obtained 4-chloromethyldihydrolutidinedicarboxylic ester in 54% yield from dichloroethyl ether and β-aminocrotonic ester in aqueous ammonia. Acetylacetonamine and benzoylacetonamine [4] give the diacetyl- and dibenzoyl-compounds :



(X = ·COOEt, ·COMe, ·COPh.)

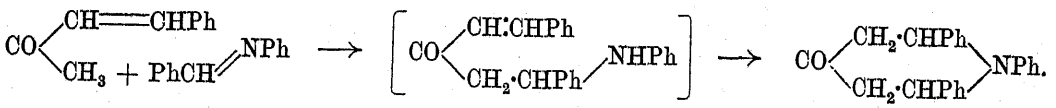
β-Aminocrotonic ester itself is converted into a pyridine derivative by the action of $POCl_3$: [5]



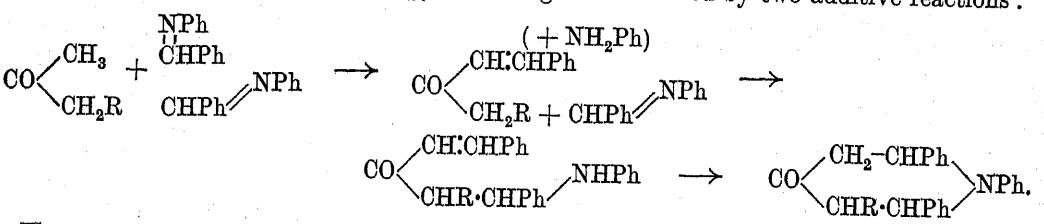
[1] v. Walther, *J. pr. Chem.*, 1903, **67**, 504.
[2] *Ber.*, 1922, **55**, 3429.
[3] *Ibid.*, 1911, **44**, 489; 1918, **51**, 569.
[4] *Ibid.*, pp. 575, 577.
[5] Michaelis, *ibid.*, 1901, **34**, 2283; 1902, **35**, 3156; 1903, **36**, 515; *Ann.*, 1909, **366**, 337.

11. From 4 : 5-unsaturated amines : $C<^{C=C}_{C-C}>NH\cdot R$

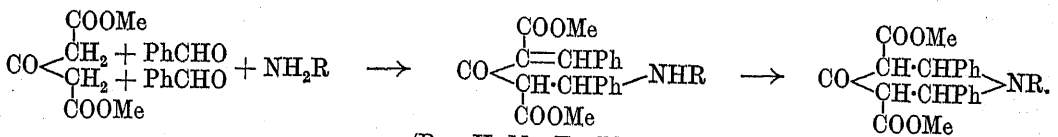
Ring-closure by intramolecular addition at the double bond probably occurs in a number of pyridine syntheses. Thus Mayer [1] obtained 1 : 2 : 6-triphenyl-4-piperidone by condensing benzalacetone (or acetone itself) with benzalaniline :



Later [2] he extended the reaction to other methyl ketones and to acetonedicarboxylic ester. The benzal derivative of the ketone is probably first formed, benzaldehyde being supplied by hydrolysis of the Schiff's base. The pyridine ring is then closed by two additive reactions :

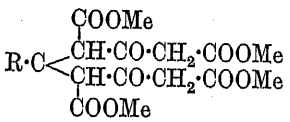


The same type of reaction occurs in Petrenko-Kritschenko's synthesis of piperidones from acetonedicarboxylic ester and benzaldehyde by the action of ammonia or primary amines at 0° : [3]



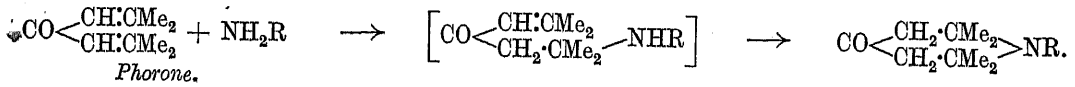
(R = H, Me, Et, Ph.)

When benzaldehyde is replaced by cinnamaldehyde or furfural no piperidone is obtained, but only the 1 : 5-diketone,



which cannot be converted into a pyridine derivative (cf. p. 210). The reaction also fails with formaldehyde.[4]

The preparation of triacetonamine from phorone and ammonia [5] is a simpler example of this type of ring-closure. Hydroxylamine yields the *N*-hydroxy-derivative : [6]

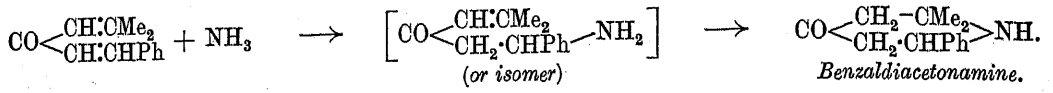


Phorone.

(R = H or ·OH.)

[1] *Bull.*, 1904, [iii], **31**, 985. [2] *Ibid.*, 1905, [iii], **33**, 498.
[3] *Ber.*, 1906, **39**, 1358; 1907, **40**, 2882; 1908, **41**, 1692; 1909, **42**, 2020, 3684, 3688, 3693; *J. pr. Chem.*, 1912, **85**, 1. [4] Ruzicka and Fornasir, *Helv. Chim. Acta*, 1920, **3**, 806.
[5] Guareschi, *Ber.*, 1895, **28**, Ref. 160. [6] Harries and Lehmann, *ibid.*, 1897, **30**, 231, 2735.

Pauly [1] applied the same method to benzalmesityl oxide :



Benzaldiacetonamine.

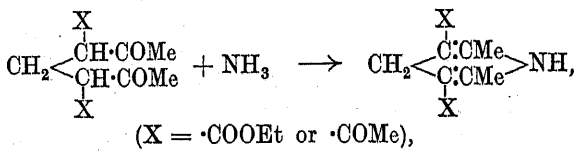
Hydrogen attached to pentavalent nitrogen, as in the salts of the unsaturated tertiary amine (I), shows no tendency to addition at a suitably placed double bond. All attempts to obtain the piperidinium compound (II) were unsuccessful : [2]



(I.) (II.)

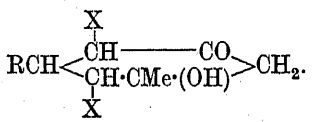
12. From 1 : 5-diketones : $C<^{CH\cdot COR}_{CH\cdot COR} + NH_2R$

Knoevenagel [3] divided 1 : 5-diketones into two classes, according as they were or were not convertible into dihydropyridines by the action of ammonia. Thus methylene*bis*acetoacetic ester [4] and methylene*bis*acetylacetone [5] readily yield dihydropyridine derivatives :

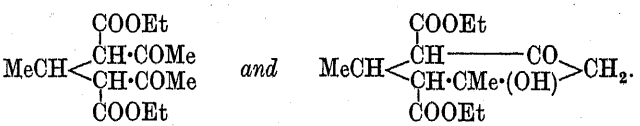


(X = ·COOEt or ·COMe),

whereas the corresponding ethylidene compounds do not. This difference was shown by Rabe [6] to be due to the fact that those so-called 1 : 5-diketones which fail to give pyridines are really to be considered as *cyclo*hexanonol derivatives,

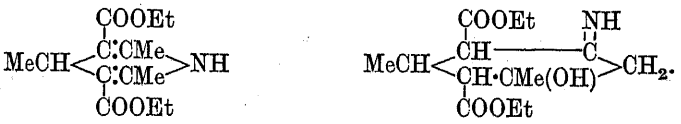


" Ethylidene*bis*acetoacetic ester " [7] is a mixture of the two isomerides,



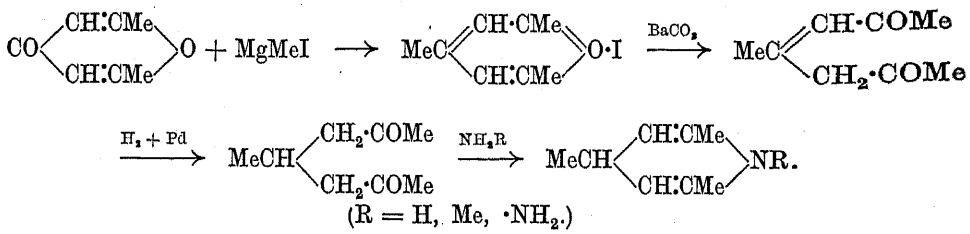
[1] *Ber.*, 1899, **32**, 2244.
[2] Valeur and Luce, *Bull.*, 1918, [iv], **23**, 184.
[3] *Ann.*, 1895, **288**, 348.
[4] Claisen, *Ber.*, 1893, **26**, 2734; Knoevenagel, *Ann.*, 1894, **281**, 95.
[5] Claisen, *loc. cit.*; Scholtz, *Ber.*, 1897, **30**, 2296; D.R.-P. 79863.
[6] *Ann.*, 1902, **323**, 83; 1904, **332**, 1.
[7] Rabe and Biilmann, *Ber.*, 1900, **33**, 3806; Rabe and Elze, *Ann.*, 1904, **332**, 19; cf. Knoevenagel and Klages, *ibid.*, 1894, **281**, 105.

The former yields dihydrocollidinedicarboxylic ester; the latter, which predominates, gives an imino-compound:

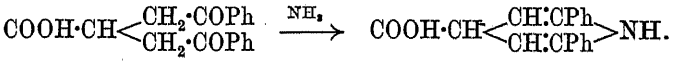


Similarly, the so-called "1 : 5-diketones" from benzaldehyde and acetoacetic ester [1] or benzoylacetic ester [2] and from acetaldehyde and benzoylacetic ester are not converted into dihydropyridines by ammonia and probably have the *cyclo*hexanonol structure.

The ethylidene*bis*acetone prepared from dimethylpyrone by v. Baeyer and Piccard [3] is, however, a true 1 : 5-diketone:

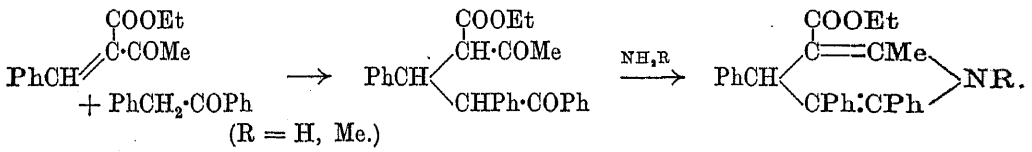


Diphenacylacetic acid [4] cannot exist in a cyclic isomeric form. It gives a dihydropyridine derivative by treatment with alcoholic ammonia:



The free pyridine acid at once loses hydrogen when liberated from its ammonium salt [5] and yields diphenyl*iso*nicotinic acid. In this case, no ring-closure occurs when ethylamine, allylamine or aniline is substituted for ammonia.

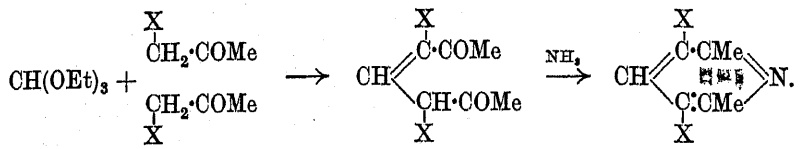
Rabe [6] obtained an *N*-methyldihydropyridine from the condensation product of desoxybenzoin and benzalacetoacetic ester by the action of methylamine. Ammonia behaves similarly: [7]



Corresponding to the formaldehyde derivatives of acetoacetic ester and acetylacetone are the methenyl compounds formed from these ketones and orthoformic ester or chloroform.

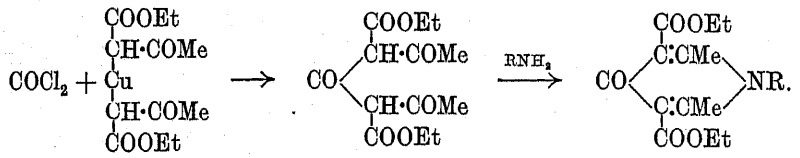
[1] Hantzsch, *Ber.*, 1885, **18**, 2585. [2] Engelmann, *Ann.*, 1885, **231**, 69. [3] *Ibid.*, 1914, **407**, 332.
[4] Paal and Strasser, *Ber.*, 1886, **19**, 3145. [5] Cf. Hantzsch, *Ann.*, 1882, **215**, 44.
[6] *Ibid.*, 1908, **360**, 275. [7] Knoevenagel, *ibid.*, 1894, **281**, 74.

Pyridines are obtained from them by the prolonged action of aqueous ammonia—two to three days at 15° : [1]



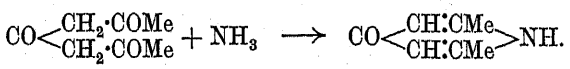
(X = ·COOEt or ·COMe.)

γ-Pyridones are obtained by the action of ammonia or primary amines upon such 1 : 3 : 5-triketones as are capable of di-enolisation. Thus Conrad and Guthzeit [2] prepared lutidone-dicarboxylic ester and its *N*-methyl- and *N*-phenyl-derivatives :

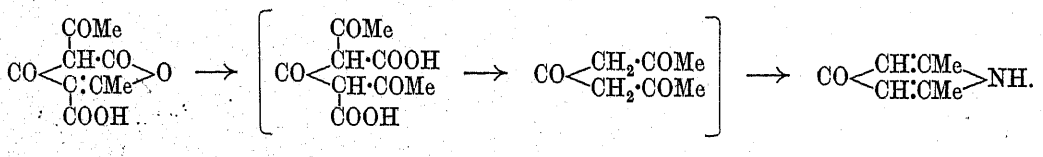


(R = H, Me, Ph.)

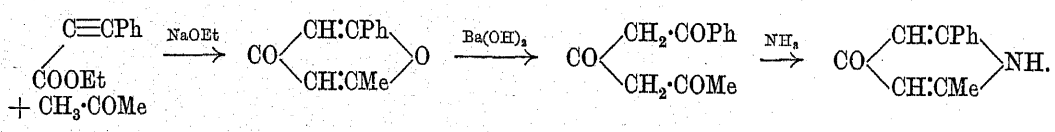
Diacetylacetone similarly yields lutidone itself : [3]



Bülow [4] in this way prepared *N*-1-triazolyl-lutidone from diacetyl-acetone and 1-amino-1 : 3 : 4-triazole. The conversion of dehydracetic acid into lutidone by the action of ammonia at 120° [5] probably proceeds *via* diacetylacetone. The yield is 67% :

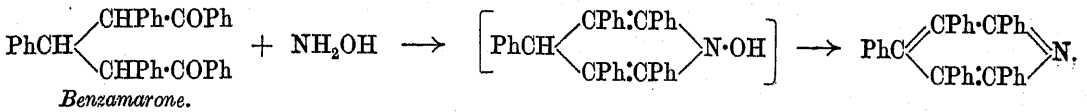


Ruhemann [6] obtained 2-phenyl-6-methyl-4-pyridone from benzoylacetylacetone and ammonia :



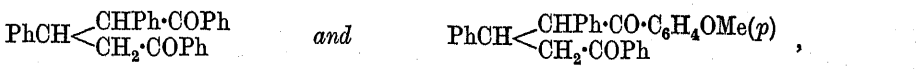
[1] Claisen, *Ber.*, 1893, **26**, 2733; *Ann.*, 1897, **297**, 39, 71; D.R.-PP. 79087, 79863.
[2] *Ber.*, 1886, **19**, 23.
[3] Feist, *Ann.*, 1890, **257**, 279.
[4] *Ber.*, 1909, **42**, 2488, 2493.
[5] Haitinger, *Monatsh.*, 1885, **6**, 105; *Ber.*, 1885, **18**, 452; Sedgwick and Collie, *J. C. S.*, 1895, **67**, 399; Michaelis and Hölken, *Ann.*, 1904, **331**, 254; v. Pechmann and Neger, *ibid.*, 1893, **273**, 207.
[6] *J. C. S.*, 1908, **93**, 1284.

The formation of a pyridine by the action of hydroxylamine upon benzamarone is apparently not a general reaction : [1]

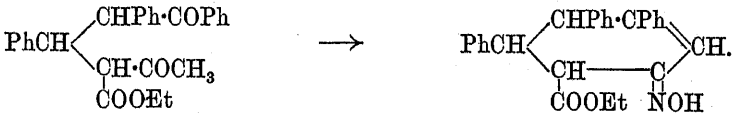


Benzamarone.

Knoevenagel [2] extended the reaction to

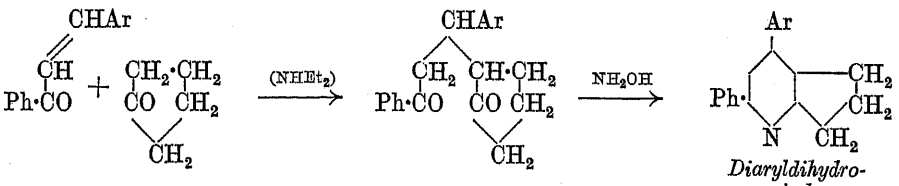


but where the terminal group is $\cdot CH_3$ the product is a *cyclo*hexenone oxime, *e.g.* :



This seems to indicate that, as in the cases mentioned above, the so-called " 1 : 5-diketone " is really a *cyclo*hexanone derivative.

Knoevenagel concluded that a pyridine is only formed when at least three aryl groups are adjacent to the two ketonic groups. This rule does not apply, however, to the series of 1 : 5-diketones obtained by Stobbe from *cyclo*pentanone or *cyclo*hexanone by condensation with benzalacetophenone, etc. : [3]

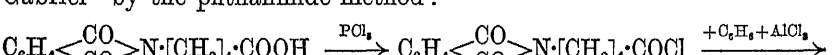


Diaryldihydropyrindene.

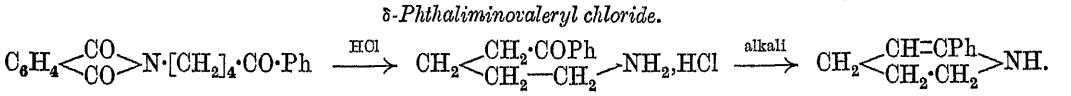
$\left(\text{Ar} = \text{Ph},\ CH_2{<}\begin{matrix}O\\O\end{matrix}{>}C_6H_3\cdot,\ \cdot p\text{-MeO}\cdot C_6H_4\cdot\right)$

13. From δ-aminoketones, etc. : C(CH·COR)(C·C)NH₂

Primary aminoketones of the type $R\cdot CO\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot NH_2$ pass at once into tetrahydropyridines when liberated from their salts. Such δ-aminoketones have been prepared by Gabriel [4] by the phthalimide method :

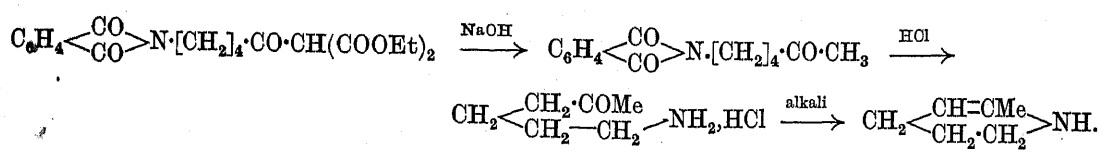


δ-Phthaliminovaleryl chloride.

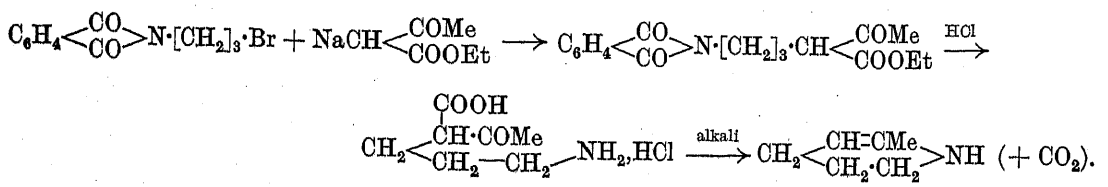


[1] Knoevenagel and Weissgerber, *Ber.*, 1893, **26**, 436. [2] *Ann.*, 1894, **281**, 33; 1898, **303**, 225.
[3] Stobbe, *Ber.*, 1902, **35**, 3973; *J. pr. Chem.*, 1912, **86**, 241. [4] *Ber.*, 1908, **41**, 2010.

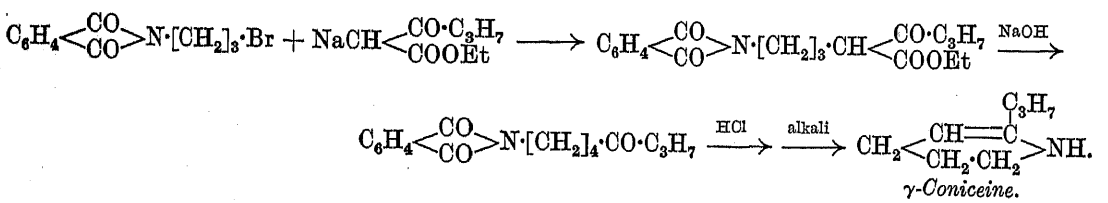
The corresponding methyltetrahydropyridine is obtained by condensing the δ-phthaliminovaleryl chloride with sodiomalonic ester and hydrolysing first with alkali and then with HCl.[1]



The same compound results more simply, but in smaller yield, from the hydrolysis of γ-phthaliminoethylacetoacetic ester :[2]

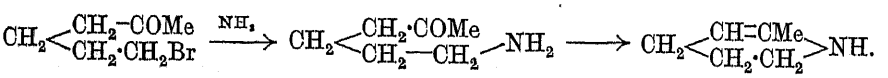


The method has been applied by Gabriel[3] to the synthesis of γ-coniceine, an alkaloid obtained first by Hofmann in 1885 from bromoconiine and alkali, and found in natural coniine by Wolffenstein ten years later :

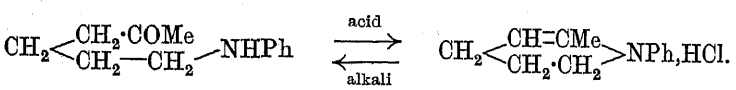


γ-*Coniceine.*

In Lipp's pyridine synthesis, δ-bromoketones are condensed with ammonia or primary amines. Thus δ-bromobutyl methyl ketone yields 6-methyltetrahydropyridine.[4]



Methylamine gives 1 : 6-dimethyltetrahydropyridine. Aniline behaves somewhat differently. The phenylaminoketone first formed is stable in the free state, but its salts are those of 1-phenyl-6-methyltetrahydropyridine. On addition of alkali the phenylaminoketone is regenerated :[5]

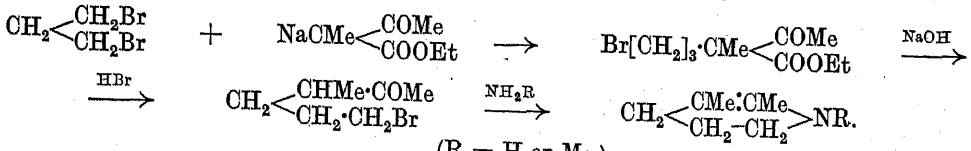


Reduction of the salt to phenylmethylpiperidine prevents regeneration of the open chain compound.

[1] Gabriel and Colman, *Ber.*, 1909, **42**, 1243. [2] Gabriel, *ibid.*, p. 1242.
[3] *Ibid.*, p. 4059. [4] Lipp, *ibid.*, 1885, **17**, 3284; 1892, **25**, 2190; *Ann.*, 1896, **289**, 198.
[5] *Idem*, *Ber.*, 1892, **25**, 2190; *Ann.*, 1896, **289**, 173.

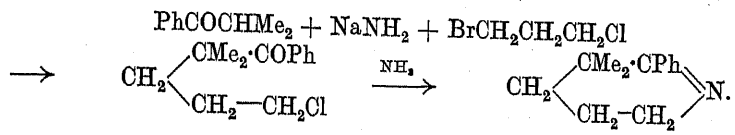
Secondary amines such as dimethylamine give only the aminoketone.*

Ladenburg [1] extended Lipp's synthesis to *N*-ethyl- and *N*-propyl-derivatives. 5 : 6-Dimethyl- and 1 : 5 : 6-trimethyl-tetrahydropyridines were prepared by Sachs : [2]

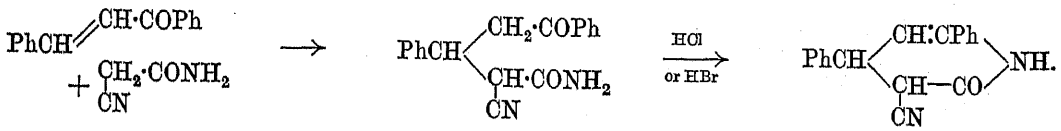


(R = H or Me.)

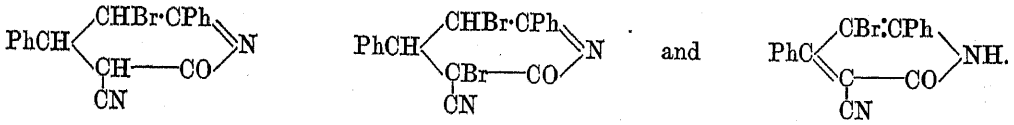
Syntheses by Lipp's method give, as has been seen, 1 : 2 : 3 : 4-tetrahydropyridines. Haller and Ramart-Lucas [3] prepared a δ-chloroketone in which enolisation was precluded. The product of the action of ammonia in this case was a 2 : 3 : 4 : 5-tetrahydropyridine :



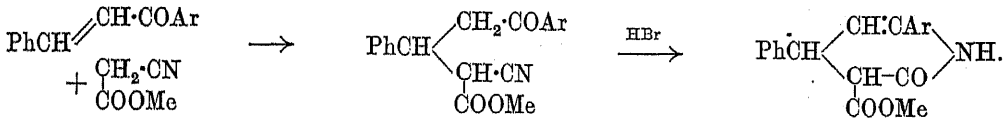
δ-Keto-amides undergo ring-closure in the presence of mineral acids. Kohler and Souther [4] condensed cyanacetamide with benzalacetophenone and obtained pyridine derivatives by the action of halogen acids or bromine upon the product :



The bromination product was a mixture of

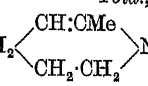
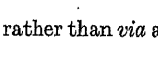


Kohler, Graustein and Merrill [5] similarly condensed cyanacetic ester with benzalacetophenone and its *p*-chloro-derivative and converted the products into pyridines :

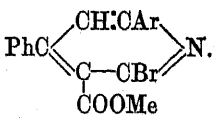


(Ar = Ph, *p*-ClC$_6$H$_4$.)

[1] *Ann.*, 1899, **304**, 54. [2] *Ber.*, 1899, **32**, 61. [3] *Ann. Chim.*, 1917, [ix], **8**, 5.
[4] *J. A. C. S.*, 1922, **44**, 2907. [5] *Ibid.*, p. 2544.

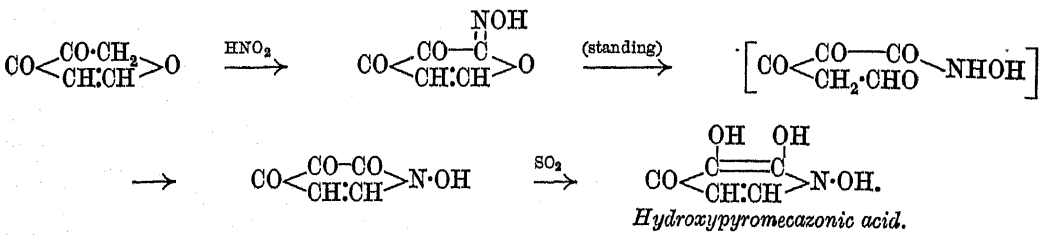
* The non-formation of a quaternary salt,  , is a further indication that the reaction proceeds *via* an aminoketone as formulated rather than *via* an ε-bromo-amine,  .

Bromination converted the condensation product into



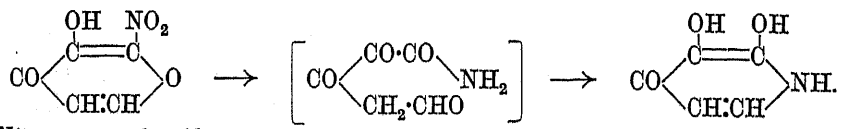
Malononitrile behaves like cyanacetic ester.[1]

The conversion of pyromeconic acid into hydroxypyromecazonic acid by reduction of its *iso*nitroso-derivative with SO_2 is an example of the same type of keto-amide ring-closure :[2]



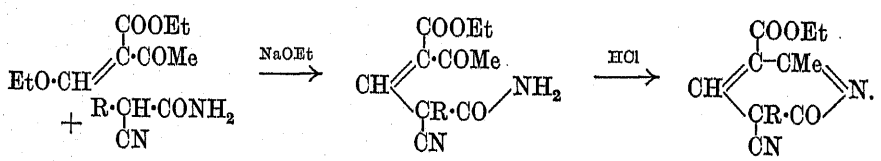
Hydroxypyromecazonic acid.

Nitropyromeconic acid is similarly reduced by SO_2 or HI to pyromecazonic acid :[3]



Nitropyromeconic acid. *Pyromecazonic acid.*

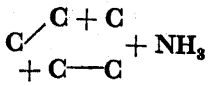
Errera's synthesis of pyridones from cyanacetamides and ethoxymethylene-acetoacetic esters may also be included here :[4]



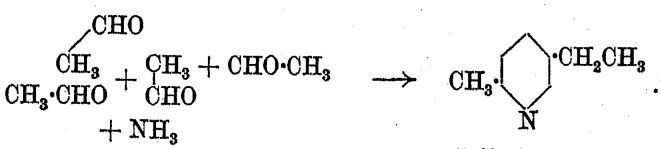
(R = H, Me.)

The yield is only small (7%).

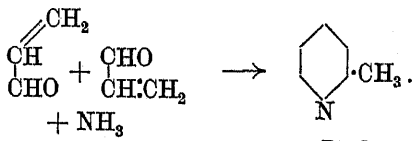
[1] Kohler and Souther, *loc. cit.*
[2] Ost, *J. pr. Chem.*, 1879, **19**, 203; Peratoner, *R. A. L.*, 1902, [v], **11**, i, 327.
[3] Ost, *J. pr. Chem.*, 1881, **23**, 439; Peratoner, *Gazz.*, 1911, **41**, ii, 619.
[4] Errera, *Ber.*, 1900, **33**, 2969, 2971; 1901, **34**, 3691.

14. From aldehyde-ammonia, etc.: 

One of the earliest pyridine syntheses was that of v. Baeyer,[1] who by heating aldehyde-ammonia obtained "aldehyde-collidine" and from acrolein-ammonia α-picoline:



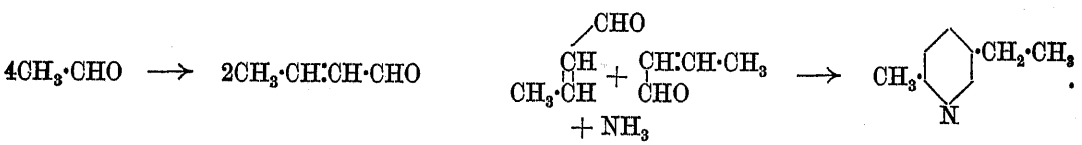
"Aldehyde-collidine."



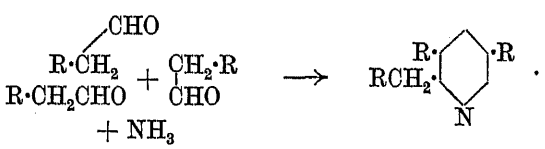
α-Picoline.

Aldehyde-collidine was also prepared by Wurtz[2] from aldol-ammonia and by Krämer[3] from ethylidene dichloride and alcoholic ammonia. The reaction was extended to propionaldehyde-ammonia,[4] and to *iso*valeraldehyde-ammonia by Ljubavin,[5] the products being "parvoline" and "valeritrine" respectively. Schiff[6] obtained "paraconiine" from butyraldehyde.

The constitution of the pyridine derivatives obtained from aldehyde-ammonias was elucidated by the investigations of Dürkopf and his co-workers.[7] Dürkopf considered that aldolisation or crotonisation first occurred, four molecules of acetaldehyde taking part for each molecule of ammonia:

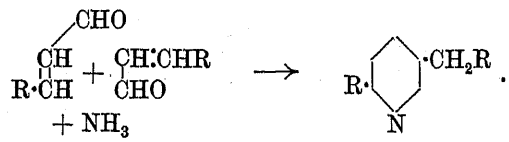


A careful study of the reaction has been made by Tschitschibabin,[8] who has found evidence for no less than five types of condensation. These are:

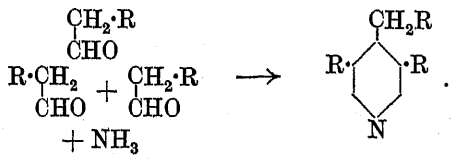
(i) 

[1] *Ann. Suppl.*, 1867, **5**, 94; *Ann.*, 1870, **155**, 281, 294; Schiff, *Ann. Suppl.*, 1868, **6**, 19; Vohl, *Jahresber.*, 1870, 807; Claus, *Ann.*, 1871, **158**, 222.
[2] *Ber.*, 1875, **8**, 1196.
[3] *Ibid.*, 1870, **3**, 257; see also Tawildarow, *Ann.*, 1875, **176**, 15.
[4] Waage, *Monatsh.*, 1882, **3**, 693; 1883, **4**, 708; Hoppe, *ibid.*, 1888, **9**, 634.
[5] *J. Russ.*, 1886, **5**, 339; 1887, **6**, 32.
[6] *Ann.*, 1873, **166**, 88.
[7] *Ber.*, 1885, **18**, 920; 1887, **20**, 444, 1660; 1888, **21**, 294, 832, 2707, 2713; 1890, **23**, 685, 1110.
[8] *J. C. S.*, Abstr. 1906, i, 451; 1915, i, 638; 1923, i, 1121, 1122, 1123.

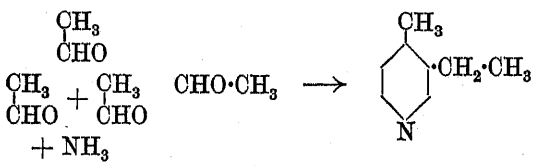
Acetaldehyde, butyraldehyde and valeraldehyde (R = H, Et, Pr) give products formed according to this scheme, which is limited, however, to saturated aldehydes.

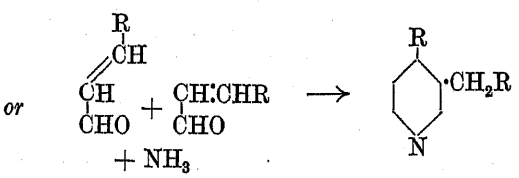
(ii) 

This is the scheme suggested by v. Baeyer (1870) and by Dürkopf and Schlaugk (1888), and applies to unsaturated aldehydes. "Aldehyde-collidine" is thus produced from acetaldehyde on account of the rapid crotonisation which takes place.

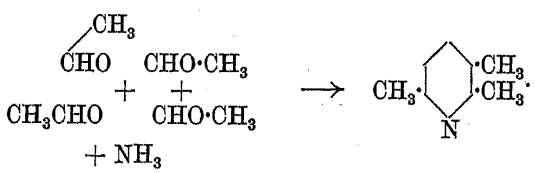
(iii) 

Acetaldehyde, for example, gives rather more γ-picoline than α-picoline (scheme i), and γ-phenylpyridine accompanies the α-phenylpyridine from a mixture of benzaldehyde, acetaldehyde and ammonia.

(iv) 

or 

A small amount of 3-ethyl-4-methylpyridine is obtained from acetaldehyde.

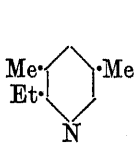
(V.) 

This scheme accounts for the production of 2 : 3 : 6-trimethylpyridine from paraldehyde and ammonia.

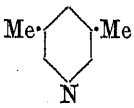
Tschitschibabin showed that satisfactory yields of pyridine bases are conveniently obtained by passing the aldehyde vapour with ammonia over granular Al_2O_2 at 200–350°. The products are the same as when the reaction is performed in a sealed tube. Acetaldehyde and ammonia at 300° gave a 60% yield of mixed bases consisting of :

α-Picoline (scheme i)	28%
γ-Picoline (scheme iii)	30%
2-Methyl-5-ethylpyridine (scheme ii)	33% (aldehyde-collidine)
4-Methyl-3-ethylpyridine (scheme iv)	6%

The total yield from propionaldehyde was 40%, the products identified being :

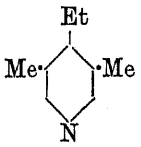


Parvoline. (60%.)



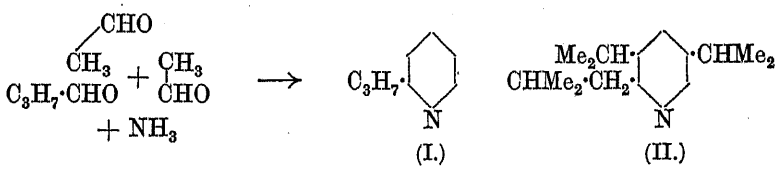
(18%.)

and



(Dürkopf and Gottsch's *second parvoline*.)

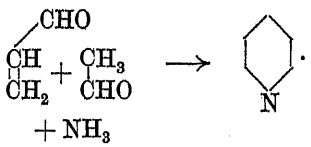
Schiff's " paraconiine " from butyraldehyde is a mixture of α-propylpyridine (I) and α-propylpiperidine, both due to the presence of acetaldehyde (scheme i)



(I.) (II.)

" Valeritrine " (II) is also formed according to scheme i.

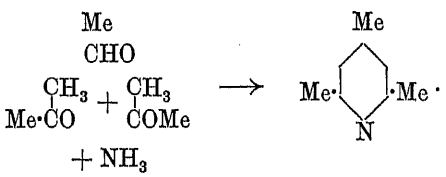
Pyridine itself is obtained by passing a mixture of acetaldehyde and acrolein over alumina (scheme ii) :



The formation of aldehyde-collidine when crotonic acid is heated with calcium chloride–ammonia at 225–230° [1] is probably due to intermediate production of acetaldehyde :

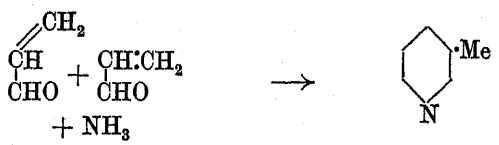
$$CH_3{\cdot}CH{:}CH{\cdot}COOH \xrightarrow{+H_2O} CH_3CHO + HCHO + CO_2.$$

According to recent patents [2] a 68% yield of aldehyde-collidine results when a mixture of paraldehyde and 10% aqueous ammonia is heated at 150–180°. If half the paraldehyde be replaced by formaldehyde the product is a mixture of equal parts of aldehyde–collidine and α-picoline; paraldehyde and acetone yield 2 : 4 : 6-trimethylpyridine : [3]

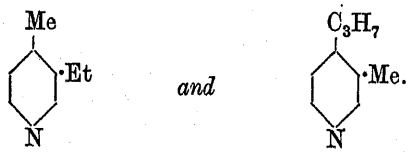


[1] Fichter and Labhardt, *Ber.*, 1909, **42**, 4714.
[2] E.P. 146869 (1917), D.R.-PP. 347820 and 349184 (1922).
[3] E.P. 147101 (1918); D.R.-P. 349267 (1922).

Other variations of the aldehyde-ammonia method may be mentioned briefly. Glycerol, phosphorus pentoxide and acetamide give a 20% yield of β-picoline free from isomeride : [1]



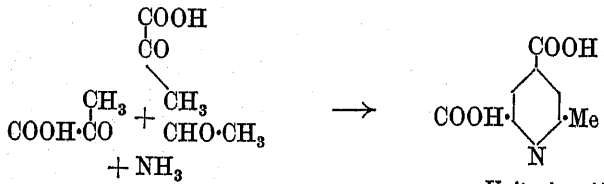
The acetyl group plays no part in the reaction, but serves to "fix" the ammonia. Probably urea would give the same result. Hesekiel [2] extended the method to acetaldehyde and propionaldehyde, which when heated with acetamide and P_2O_5 at 160° gave respectively :



The structures assigned to these products are open to some doubt.

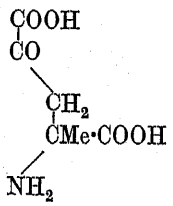
Stöhr [3] obtained a small amount of pyridine by distilling glycerol with ammonium phosphate. The addition of P_2O_5 to this mixture gives β-picoline in fairly good yield.[4] Pyridine bases have also been obtained from glycerol by heating with ammonium sulphate,[5] ammonium chloride [6] or zinc chloride-ammonia.[7]

To this group of pyridine syntheses belongs also the preparation of "uvitonic acid" by Böttinger [8] from pyruvic acid and ammonia. The constitution of the product was elucidated by Altar.[9] Part of the pyruvic acid loses CO_2, giving acetaldehyde, and in fact the addition of acetaldehyde to the mixture improves the yield of uvitonic acid :



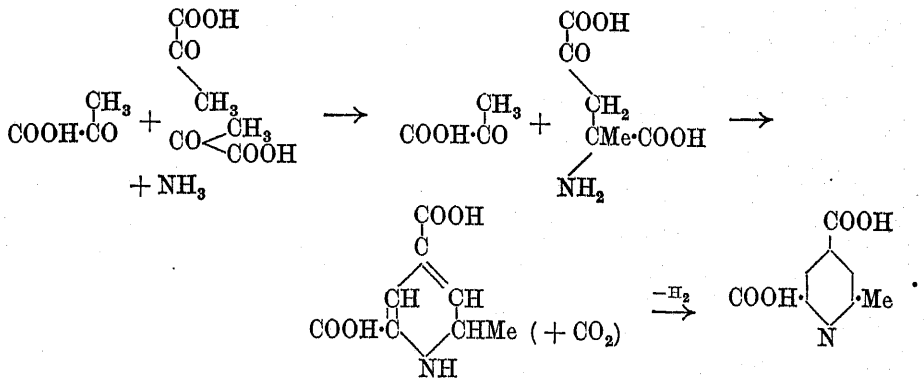
Uvitonic acid.

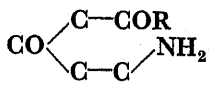
de Jong [10] gives a slightly different explanation of the reaction. An aqueous solution of ammonium pyruvate after two or three days' exposure to air is found to contain the amino-acid,



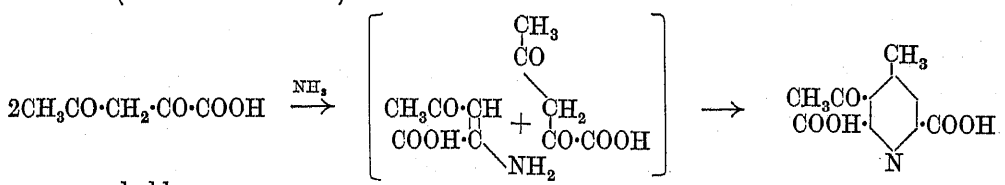
[1] Zanoni, *Ber.*, 1882, **15**, 528; Hesekiel, *ibid.*, 1885, **18**, 911, 3091. [2] *Ibid.*, p. 3095.
[3] *J. pr. Chem.*, 1892, **45**, 23. [4] Ladenburg, *Ber.*, 1890, **23**, 2688; Schwarz, *ibid.*, 1891, **24**, 1676.
[5] Storch, *ibid.*, 1886, **19**, 2456. [6] Etard, *Compt. rend.*, 1881, **92**, 460, 795.
[7] Storch, *loc. cit.* [8] *Ann.*, 1877, **188**, 329; 1881, **208**, 139; *Ber.*, 1880, **13**, 2032, 2049; 1881, **14**, 67.
[9] *Ann.*, 1887, **237**, 197. [10] *Rec. trav. chim.*, 1903, **23**, 131.

which eventually passes into uvitonic acid. The change occurs more rapidly when ammonium pyruvate solution is boiled with excess of ammonia :

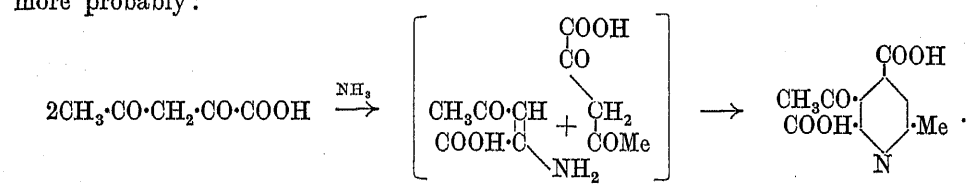


15. From acylpyruvic esters, $RCO{\cdot}CH_2{\cdot}CO{\cdot}COOEt$: 

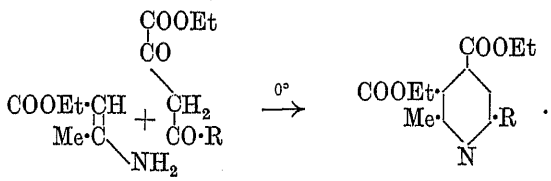
This is an extension of Böttinger's uvitonic acid synthesis from pyruvic acid and ammonia. Mumm and Bergell [1] obtained a pyridine derivative by the action of ammonia upon acetylpyruvic acid (acetone-oxalic acid) :



or, more probably :



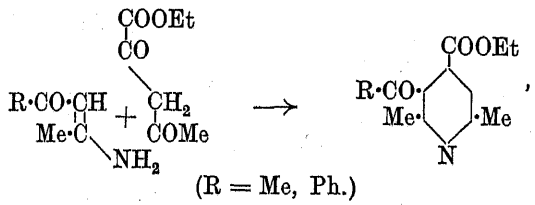
The reaction was extended by Mumm and Hüneke [2] to the condensation of β-aminocrotonic ester with acetylpyruvic ester and by Mumm and Böhme [3] to other acylpyruvic esters :



(R = Me, Et, ·C_3H_7, ·$CHMe_2$, ·CMe_3, Ph.)

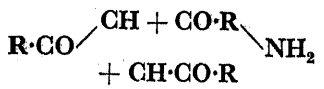
[1] *Ber.*, 1912, **45**, 3041. [2] *Ibid.*, 1917, **50**, 1573. [3] *Ibid.*, 1921, **54**, 726.

The yields are 80–90% of the theoretical. The β-aminocrotonic ester may be replaced by the ammonia derivative of acetylacetone or of benzoylacetone : [1]

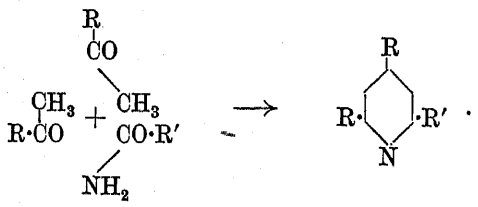


(R = Me, Ph.)

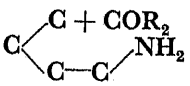
the yields here being 65% and 60% respectively. β-Aminocrotonic ester fails to give pyridines when condensed with acetylacetone, oxalacetic ester or formylacetone.

16. From acid amides and ketones : 

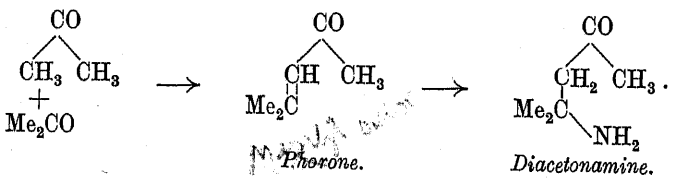
Pictet and Stehelin [2] have obtained alkylated pyridines by heating acid amides with ketones at 250–280°. The acyl group in this case takes part in the ring formation :



Acetone and acetamide (R = R′ = Me) give only a small amount of trimethylpyridine, but the yield is better with acetophenone and benzamide (R = R′ = Ph). Acetaldehyde and formamide (R = R′ = H) fail to give pyridine, and from acetaldehyde and acetamide (R = H, R′ = Me) very little α-picoline is obtained.

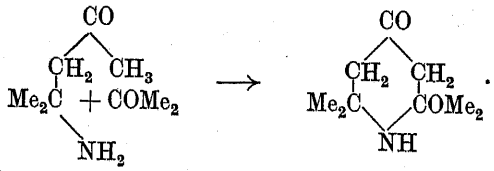
17. Triacetonamines : 

The action of ammonia on acetone was studied independently by Heintz [3] and by Sokolov and Latschinov.[4] The products are diacetonamine and triacetonamine :



Phorone. *Diacetonamine.*

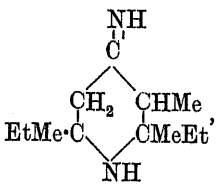
[1] Mumm and Böhme, *loc. cit.*
[2] *Compt. rend.*, 1916, **162**, 876.
[3] *Ann.*, 1874, **174**, 144; 1875, **178**, 305.
[4] *Ber.*, 1874, **7**, 1384.



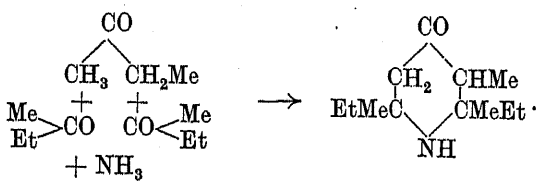
Diacetonamine+acetone. *Triacetonamine.*

The yield of triacetonamine obtained in this way is only about 1%,[1] but from phorone and ammonia much better yields result.[2] On reduction, triacetonamine is converted into the corresponding secondary alcohol—an alkamine.[3]

Thomae [4] from methyl ethyl ketone obtained an oxygen-free compound which was shown by Traube [5] to be the imino derivative,

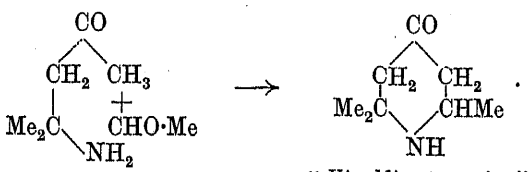


and not EtMeC:N·CMeEt·N:CMeEt, as Thomae suggested. Traube prepared the piperidone in 25% yield in alcoholic solution :



The reaction even in alcohol is very slow and requires two to three weeks.

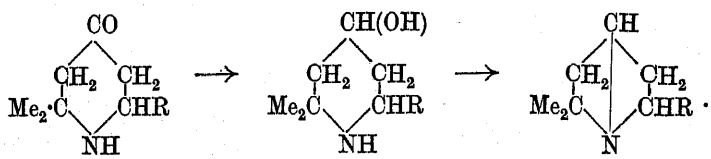
In place of a third molecule of acetone a molecule of aldehyde may be used. Thus diacetonamine combines with acetaldehyde to give " vinyldiacetonamine," [6] which was shown by Fischer [7] to be entirely analogous to triacetonamine :



" Vinyldiacetonamine."

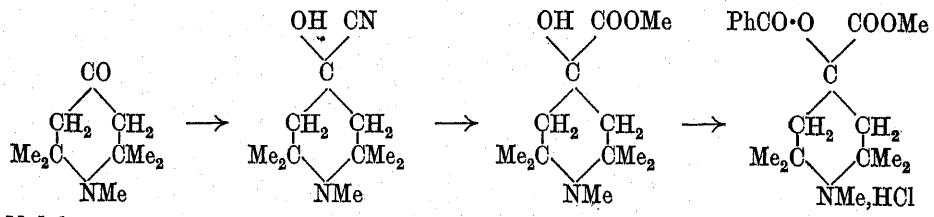
[1] E. Fischer, *Ber.*, 1883, **16**, 649, 1604; 1884, **17**, 1789.
[2] Guareschi, *ibid.*, 1894, Ref. **28**, 160; Pauly, *Ann.*, 1902, **322**, 77.
[3] Heintz, *ibid.*, 1876, **183**, 303; Fischer, *loc. cit.*; Clarke and Francis, *Ber.*, 1912, **4**, 2060.
[4] *Arch. Pharm.*, 1905, **243**, 294, 393.
[5] *Ber.*, 1908, **41**, 777.
[6] Heintz, *Ann.*, 1877, **189**, 214.
[7] *Loc. cit.*

Benzaldehyde,[1] *iso*butyraldehyde, cinnamaldehyde, anisaldehyde, nitrobenzaldehyde and *p*-hydroxybenzaldehyde react with diacetonamine in the same way.[2] The products give alkamines on reduction, and these are dehydrated readily to form " acetonines "—tetrahydropyridines :[3]

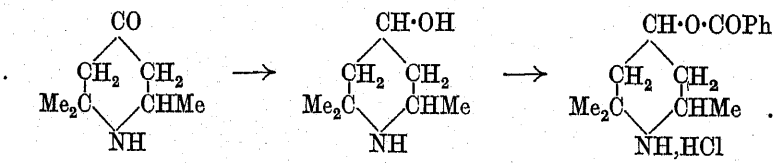


Acetonamine. *Alkamine.* *Acetonine.*

The discovery of the hypnotic properties of the alkamines led to a large number of patents for the preparation of these compounds and their derivatives. The reduction of triacetonamine, vinyldiacetonamine, benzylidene- and piperonylidene-diacetonamines to the corresponding alkamines electrolytically or by sodium amalgam or aluminium amalgam is claimed in D.R.-PP. 95621–95623, 96539 and 96362. The two eucaines are benzoic esters of alkamines :[4]



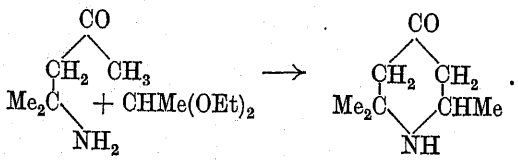
N-*Methyltriacetonamine.* *α-Eucaine.*



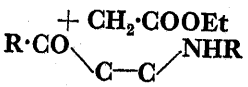
β-Eucaine.

Euphthalmine[5] is the corresponding mandelyl derivative of *N*-methyl-vinyldiacetonalkamine hydrochloride.

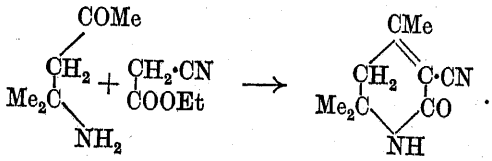
King, Mason and Schryver[6] have prepared vinyldiacetonamine from diacetonamine and acetal in alcoholic solution. A yield of 90% is claimed :



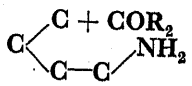
[1] Heintz, *Ann.*, 1878, **193**, 62.
[2] Antrick, *ibid.*, 1885, **227**, 365.
[3] Fischer, *loc. cit.*
[4] D.R.-PP. 90245, 97672.
[5] D.R.-P. 95680.
[6] E.P. 101738.

18. From diacetonamine and cyanacetic ester: 

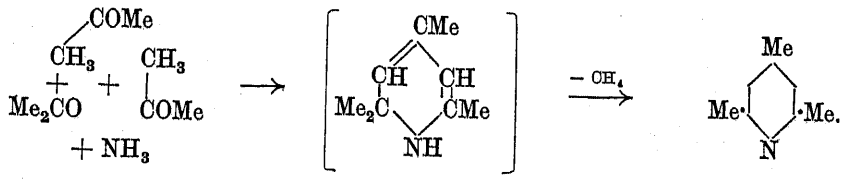
The condensation of diacetonamine with cyanacetic ester at 0° yields a dihydropyridone:[1]



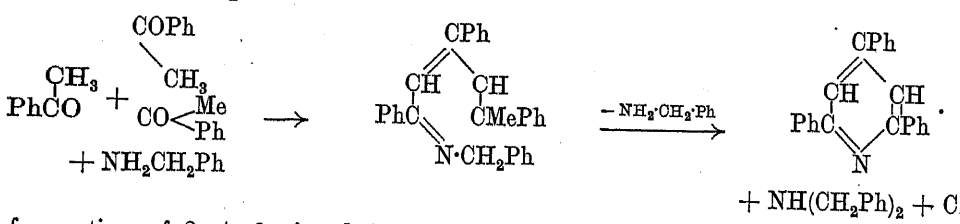
The diacetonamine may be replaced by acetone or mesityl oxide in the presence of ammonia,[2] and methylamine, benzylamine, allylamine, camphylamine and ethylenediamine have been used instead of ammonia for the production of *N*-substituted derivatives.[3]

19. From ketones and ammonia (Riehm's method): 

By heating acetone and ammonium chloride at a high temperature in a sealed tube Riehm[4] obtained 2 : 4 : 6-trimethylpyridine together with CH_4.



Acetophenone in the same way gave triphenylpyridine, which Engler and Heine[5] had earlier prepared from acetophenone, ammonia and P_2O_5. The constitution of the product was confirmed by Reddelien,[6] who obtained it by an equally curious reaction from acetophenone and benzylamine in the presence of $ZnCl_2$ or HBr:

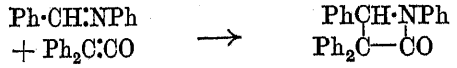


The formation of 2 : 4 : 6-trimethylpyridine from dimethylacrylic acid, $CMe_2{:}CH{\cdot}COOH$, by the action of zinc chloride-ammonia at 230°[7] is doubtless preceded by hydrolysis of the acid to acetone.

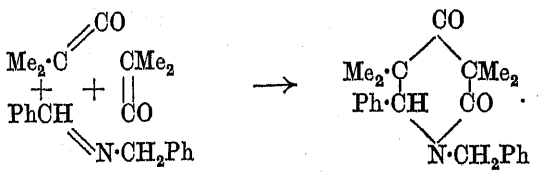
[1] Guareschi, *J. C. S.*, Abstr. 1893, i, 484; *Ber.*, 1893, Ref. 943; *Zentr.*, 1893, ii, 648.
[2] Pasquali, *ibid.*, 1897, i, 903.
[3] Guareschi, *loc. cit.* [4] *Ann.*, 1887, **238**, 16, 17. [5] *J. C. S.*, 1873, **28**, 1036.
[6] *Ber.*, 1920, **53**, 334; see also Dilthey and Kiefer, *ibid.*, p. 621.
[7] Fichter and Labhardt, *ibid.*, 1909, **42**, 4714.

20. From ketens:

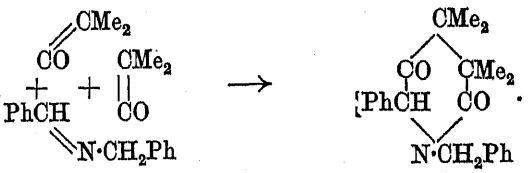
Ketens of the type $R_2C{:}CO$ form additive compounds with Schiff bases in two ways. Usually the product is a β-lactam:



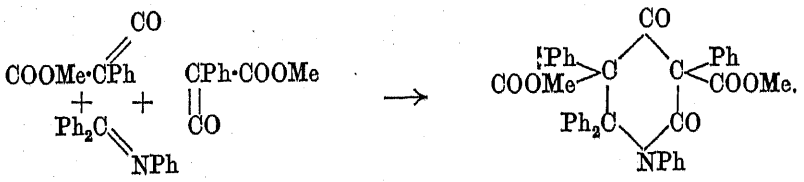
but with certain bases, especially with benzalmethylamine and benzalbenzylamine, a 2 : 4-diketopiperidine is formed: [1]



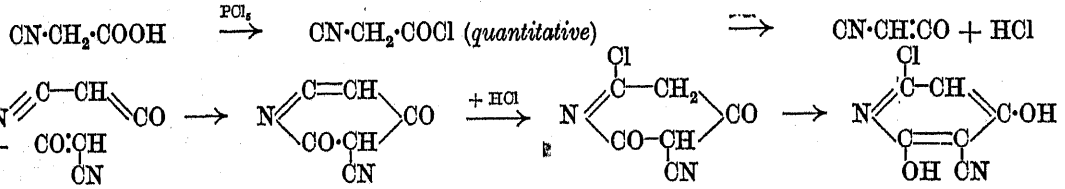
A 2 : 5-isomeride is also produced at the same time in small quantity:



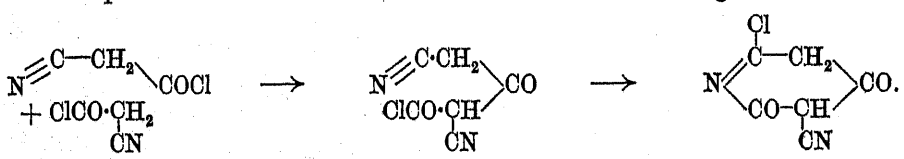
The keten, $CO{:}CPh{\cdot}COOMe$ (which is not generally included amongst keto-ketens), forms a 2 : 4-diketopiperidine with benzophenone anil:



The spontaneous decomposition of cyanoacetyl chloride at 0° yields a pyridine compound which may be regarded as derived from cyanoketen: [2]

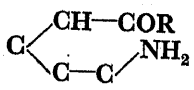


An alternative explanation involves the addition of $\cdot COCl$ at a $C{:}N$ linkage:

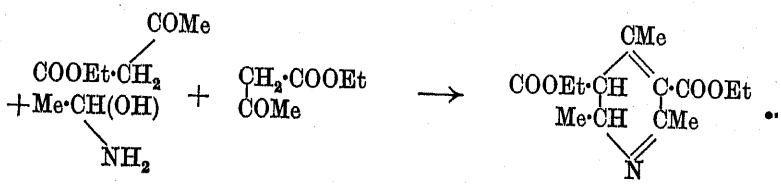


[1] Staudinger, *Ann.*, 1910, **374**, 25, 36; *Ber.*, 1917, **50**, 1041.
[2] Schroeter and Seidler, *J. pr. Chem.*, 1922, **105**, 165.

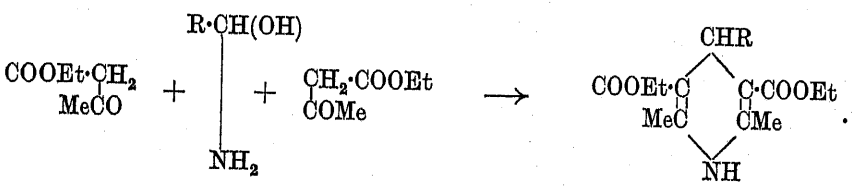
21. Hantzsch's method (acetoacetic ester etc. an aldehyde and ammonia):



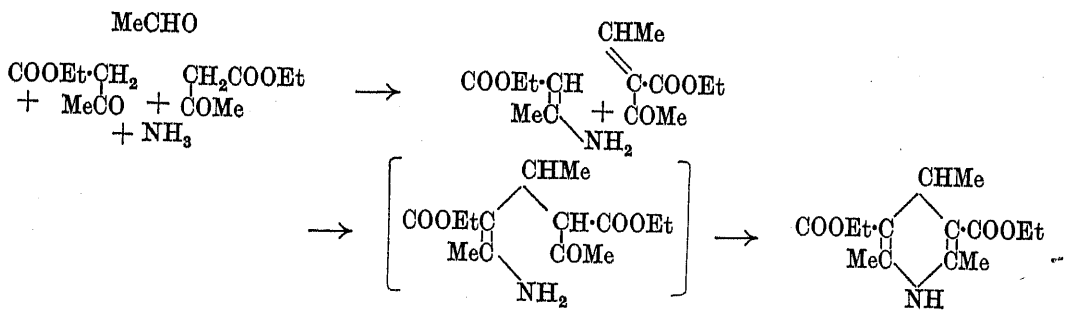
The Hantzsch synthesis consists in the condensation of two molecular proportions of acetoacetic ester with one of an aldehyde-ammonia. Thus acetaldehyde-ammonia and acetoacetic ester give dihydrocollidinedicarboxylic ester,[1] which was at first supposed to be formed in the following manner:



The extension of the reaction to other aldehydes soon showed, however, that the radical of the aldehyde molecule takes the γ- not the α-position,[2] and the reaction was figured thus:

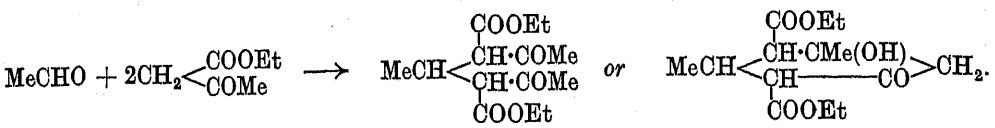


The actual mechanism of the reaction was first suggested by C. Beyer [3] and confirmed by Knoevenagel,[4] who showed that β-aminocrotonic ester and (to take the case of acetaldehyde) ethylidene-acetoacetic ester are first formed, and that these products readily condense to give dihydrocollidinedicarboxylic ester:



[1] Hantzsch, *Ann.*, 1882, **215**, 1–82; *Ber.*, 1883, **16**, 1946; Michael, *Ann.*, 1884, **225**, 121.
[2] Hantzsch, *Ber.*, 1885, **18**, 1744, 2579.
[3] *Ber.*, 1891, **24**, 1662.
[4] *Ibid.*, 1898, **31**, 738.

As by-product there is obtained the γ-diketone (or *cyclo*hexanolone, see p. 210):



When benzoylacetic ester is substituted for acetoacetic ester the γ-diketone is the only product.

Knoevenagel[1] showed that the three components may be combined in several different ways before condensation, and so long as the intermediate formation of β-aminocrotonic ester and of an alkylidene- or arylidene-acetoacetic ester is not precluded, the reaction proceeds normally with the production of a 4-substituted dihydrolutidinedicarboxylic ester. The different methods of presenting the components are:

(*a*) 2 mols. acetoacetic ester
+ aldehyde + ammonia.

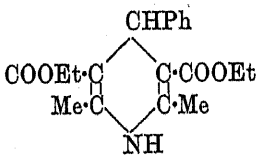
(*b*) 2 mols. acetoacetic ester
+ aldehyde-ammonia (or, in the aromatic series, a hydrobenzamide).

(*c*) 2 mols. β-aminocrotonic ester
+ aldehyde.

(*d*) acetoacetic ester + alkylidene- or arylidene-acetoacetic ester
+ ammonia.

(*e*) β-aminocrotonic ester
+ alkylidene- or arylidene-acetoacetic ester.

It will be observed that the aldehyde must *not* be in combination with both molecules of acetoacetic ester (see 1 : 5-diketones, p. 210). β-Aminocrotonic ester may, of course, be used in place of acetoacetic ester in any of the above combinations. The relative yields are seen from the following figures for the preparation of

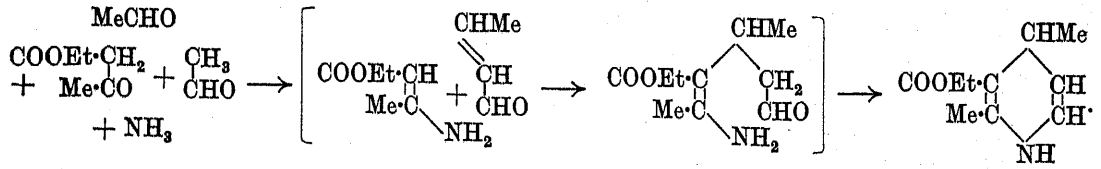


given by Knoevenagel:

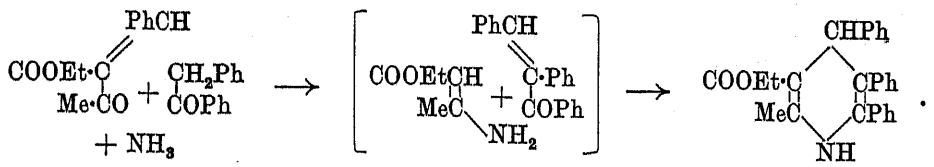
Benzaldehyde + 2 mols. β-aminocrotonic ester at 100°	Quantitative
Benzaldehyde + acetoacetic + β-aminocrotonic ester at 100°	85%
Hydrobenzamide + acetoacetic + β-aminocrotonic ester at 100°	80%
Benzalacetoacetic ester + β-aminocrotonic ester:	
at 15° (48 hours)	75%
at 100° (1 hour)	75%

[1] *Ber.*, 1898, **31**, 738.

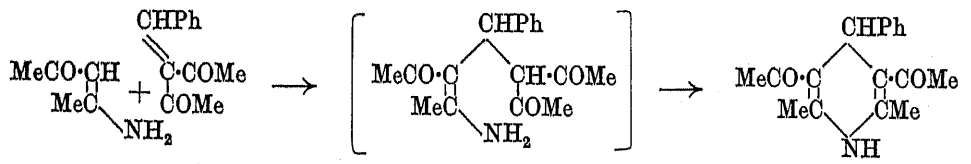
In Michael's modification of the Hantzsch synthesis one of the molecules of acetoacetic ester is replaced by an additional molecule of acetaldehyde.[1] The mechanism is precisely similar:



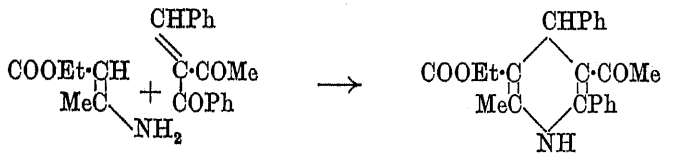
The product in this case very readily loses two atoms of hydrogen and gives 2 : 4-dimethyl-nicotinic ester. Knoevenagel similarly condensed benzalacetoacetic ester with desoxybenzoin and ammonia:[2]



The reaction was further extended by Knoevenagel and Ruschhaupt[3] to β-diketones and their ammonia derivatives. Thus benzalacetylacetone condenses with acetylacetonamine to give 4-phenyl-3 : 5-diacetyldihydrolutidine:



β-Aminocrotonic ester and benzalbenzoylacetone give, in 40–50% yield, the corresponding dihydropyridine:



Here, as in other condensations of benzalbenzoylacetone, the PhCO· rather than the MeCO· is the reactive (*i.e.* the enolisable) group, and hence Ph and not Me appears in the α-position in the product.

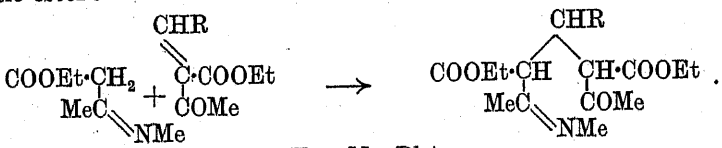
An examination of the mechanism given above for all these reactions suggests the possibility that some cases might be found in which the acetonamine or aminocrotonic ester reacts in its *imine* form,

$$R\cdot CH_2\cdot CMe{:}NH.$$

If the nitrogen atom carries a methyl (or other) group the intermediate product can no longer undergo ring-closure. Knoevenagel[4] has recorded cases of this kind. Thus β-methyl-

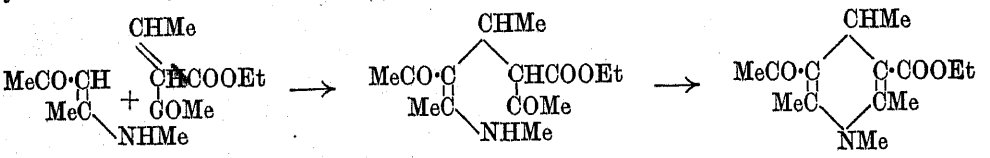
[1] *Ber.*, 1885, **18**, 2020. [2] *Ann.*, 1894, **281**, 74. [3] *Ber.*, 1898, **31**, 1025. [4] *Ibid.*, 1903, **36**, 2185–2189.

aminocrotonic ester forms no dihydropyridine derivative when condensed with ethylidene- or benzal-acetoacetic ester:

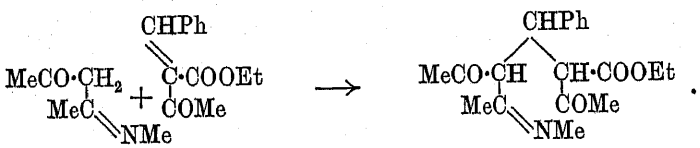


(R = Me, Ph.)

Acetylacetonemethylamine condenses normally with ethylidene-acetoacetic ester,



but with benzalacetoacetic ester it forms only the additive product:



In the following list of pyridine syntheses by Hantzsch's method the three components are set out separately, but it is to be understood that these may be employed in any of the combinations mentioned by Knoevenagel (see above).

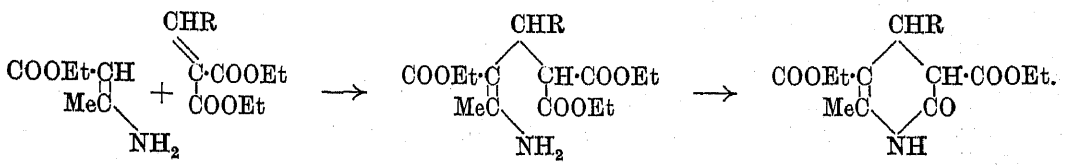
β-*Keto-ester, etc.*	*Aldehyde*, RCHO.	*Amine.*	*References.*
2 mols. of acetoacetic ester.	H·CHO	NH_3	10, 12, 13, 16
		NH_2Me	4, 5
	Me·CHO	NH_3	1, 2, 3, 5, 11, 14, 17
		NH_2Me	5, 18
	Et·CHO	NH_3	8
	$CHMe_2$·CHO	NH_3	8
	$CHMe_2$·CH_2·CHO	NH_3	8
	Ph·CHO	NH_3	5, 11, 14
		NH_2Me	18
	m-NO_2·C_6H_4·CHO	NH_3	9
	p-Me_2N·C_6H_4·CHO	NH_3	19
	PhCH:CH·CHO	NH_3	7
	Furfural	NH_3	17
	Acrolein	NH_3	8 (fails)
2 mols. of benzoylacetic ester.	Me·CHO	NH_3	11, 14
		NH_2Me	11
2 mols. of acetylacetone.	Me·CHO	NH_3	15
		NH_2Me	15
	Ph·CHO	NH_3	15
2 mols. of benzoylacetone.	Ph·CHO	NH_3	18
1 mol. of acetoacetic ester *with*:			
1 mol. of acetaldehyde.	Me·CHO	NH_3	6
1 mol. of desoxybenzoin.	Ph·CHO	NH_3	12
1 mol. of acetylacetone.	Me·CHO	NH_2Me	18
		NH_3	15
	Ph·CHO	NH_2Me	18 (fails)
1 mol. of benzoylacetone.	Ph·CHO	NH_3	18

References.

[1] Hantzsch, *Ann.*, 1882, **215**, 1–82. [2] *Idem*, *Ber.*, 1883, **16**, 1946. [3] Michael, *Ann.*, 1884, **225**, 121. [4] Kuckert, *Ber.*, 1885, **18**, 620. [5] Hantzsch, *Ber.*, 1885, **18**, 1744, 2579. [6] Michael, *ibid.*, p. 2020. [7] Epstein, *Ann.*, 1885, **231**, 3. [8] Engelmann, *ibid.*, pp. 38, 47, 56. [9] D.R.-P. 42295 (1887). [10] Griess and Harrow, *Ber.*, 1888, **21**, 2740. [11] Beyer, *ibid.*, 1891, **24**, 1662. [12] Knoevenagel, *Ann.*, 1894, **281**, 74, 77, 95. [13] Schiff and Prosio, *Gazz.*, 1895, **25**, ii, 65. [14] Knoevenagel, *Ber.*, 1898, **31**, 738. [15] Knoevenagel and Ruschhaupt, *ibid.*, p. 1025. [16] Knoevenagel, *ibid.*, 1902, **35**, 1791. [17] Ruhemann, *J. C. S.*, 1903, **83**, 377. [18] Knoevenagel, *Ber.*, 1903, **36**, 2180–2190. [19] Hinkel and Cremer, *J. C. S.*, 1920, **117**, 137.

22. From β-aminocrotonic ester etc. with malonic ester and aldehydes : $C<^{C\cdot COOEt}_{C\text{———}C}>NH_2$

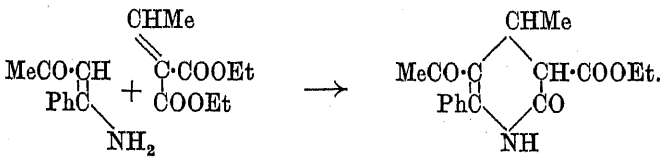
This modification of the Hantzsch synthesis was introduced by Knoevenagel and Fries,[1] who substituted malonic ester for one of the molecules of acetoacetic ester. Thus β-aminocrotonic ester and benzalmalonic ester give a 75% yield of the corresponding dihydropyridone. Ethylidenemalonic ester reacts similarly :



(R = Me or Ph.)

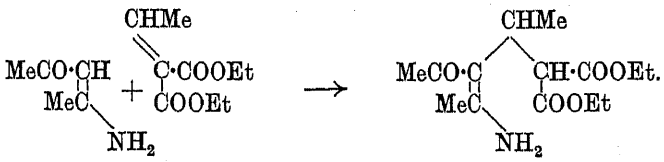
Cuminalmalonic ester is hydrolysed and only a quinoline is produced.[2]

Benzoylacetonamine reacts normally with ethylidenemalonic ester : [3] *



(60–70% yield.)

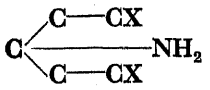
In the case of acetylacetonamine only the additive product is formed, no ring-closure taking place :



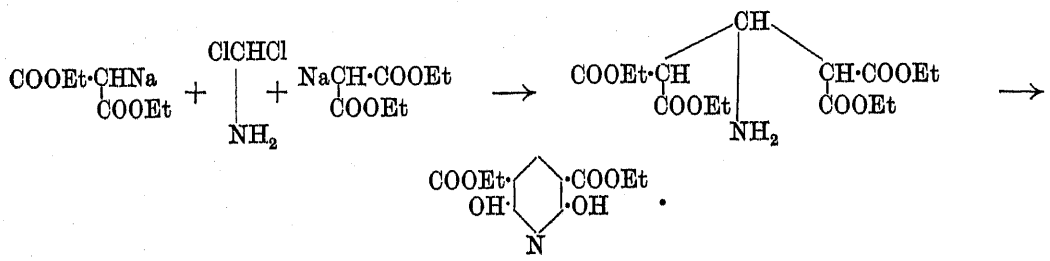
Malonic ester itself reacts rather differently with β-aminocrotonic ester (see section 24).

[1] *Ber.*, 1898, **31**, 762. [2] Knoevenagel and Brunswig, *ibid.*, 1902, **35**, 2178.
[3] Knoevenagel, *ibid.*, 1903, **36**, 2180.
* The constitution of benzoylacetonamine and hence of the product is not known with certainty.

23. Gattermann and Skita's method :

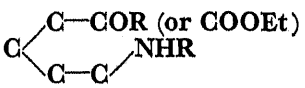


Gattermann and Schnitzspahn [1] showed that when HCl gas is passed into anhydrous HCN in acetic ester solution the product is $NH{:}CH{\cdot}NH{\cdot}CHCl_2,HCl$, which reacts as $NH_2{\cdot}CHCl_2$. For example, with sodiomalonic ester it gives a 50% yield of 2 : 6-dihydroxypyridine-3 : 5-dicarboxylic ester : [2]

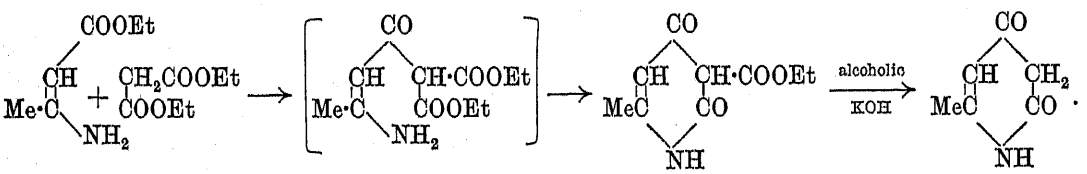


As will be observed, this method is in effect a modification of the Hantzsch synthesis (p. 227).

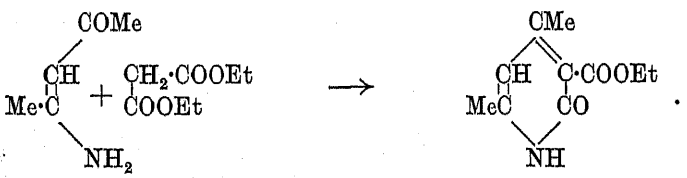
24. From β-aminocrotonic ester etc. and malonic ester etc. :



Certain syntheses are grouped here which differ from the Hantzsch method in that the intermediate is formed, not by addition, but by elimination of alcohol or water. Malonic ester condenses with β-aminocrotonic ester in the presence of NaOEt to give a dihydroxy-picoline-carboxylic ester (75% yield) which on hydrolysis with alcohol KOH is converted into 4 : 6-dihydroxy-2-methylpyridine : [3]

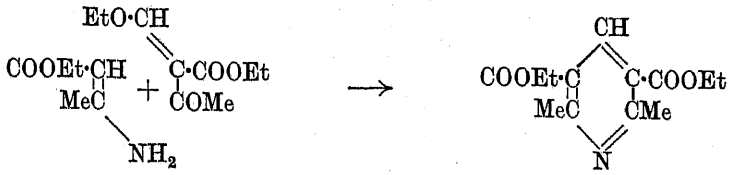


Acetylacetonamine and malonic ester similarly yield 2 : 4-dimethyl-6-pyridone-5-carboxylic ester : [4]

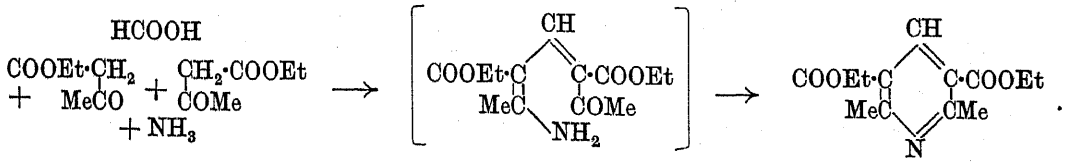


[1] *Ber.*, 1898, **31**, 1770.
[2] Gattermann and Skita, *ibid.*, 1916, **49**, 496.
[3] Knoevenagel and Fries, *ibid.*, 1898, **31**, 768.
[4] Knoevenagel and Cremer, *ibid.*, 1902, **35**, 2893.

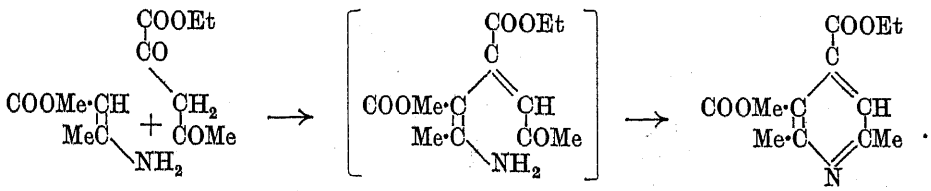
Claisen [1] obtained lutidinedicarboxylic ester from β-aminocrotonic and ethoxymethylene-acetoacetic esters :



The same product results when acetoacetic ester is condensed with ammonium formate :

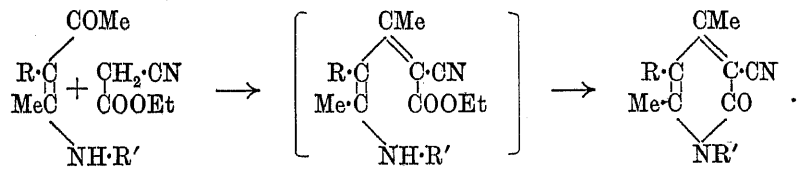


Mumm and Gottschaldt [2] have recently obtained a lutidine-3 : 4-dicarboxylic ester in 75% yield by condensing β-aminocrotonic ester with acetone-oxalic ester at the ordinary temperature :



Other syntheses from β-aminocrotonic ester are mentioned on pp. 208, 227, 231, 237.

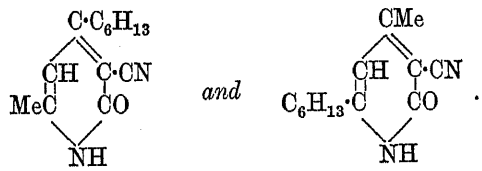
Guareschi [3] synthesised a number of α-pyridones by condensing cyanacetic ester with β-diketones (or their ammonia derivatives) in the presence of ammonia or primary amines : [4]



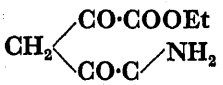
(R = H, Me; R′ = H, Me, Et, CH_2:CH·CH_2.)

The reaction fails in the case of hydroxylamine.

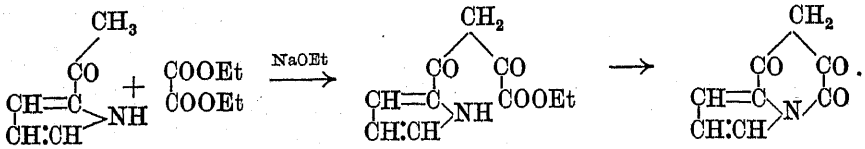
A mixture of heptoylacetone, cyanacetic ester and ammonia yields the two isomeric products :

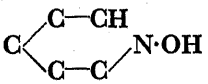


[1] *Ber.*, 1893, **26**, 2729. [2] *Ibid.*, 1922, **55**, 2067. [3] *Zentr.*, 1899, ii, 280.
[4] See also Moir, *J. C. S.*, 1902, **81**, 100.

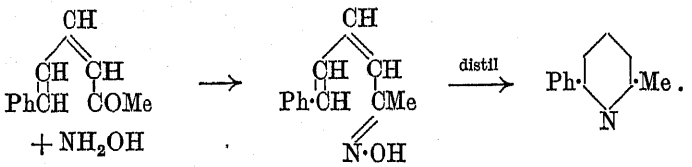
25. From α-aminoketones and oxalic ester: 

The pyrropyridine obtained by Angeli [1] from α-acetylpyrrole by condensation with oxalic ester in the presence of NaOEt is the only example of this type of pyridine synthesis:

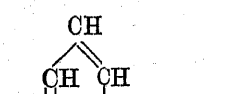


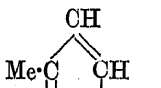
26. From oximes of unsaturated ketones: 

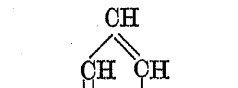
This method is due to Scholtz,[2] who obtained a 25% yield of 2-phenyl-6-methylpyridine by distillation of cinnamylidene-acetoxime:



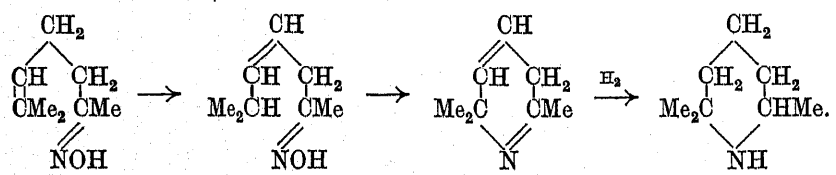
The presence of an aryl group in the δ-position to the ketonic ·CO· appears to be necessary. Pyridines have been prepared in this way from the oximes of the following ketones: [3]


(R = Me, Ph, *p*-C_7H_7·, *p*-MeO·C_6H_4·, α-$C_{10}H_7$ or *n*-C_9H_{19}·.)


(R = Me, Ph.)

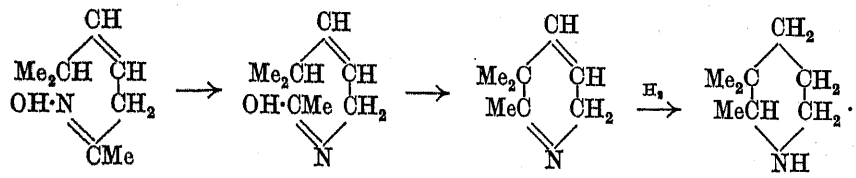

(Ar = *p*-C_7H_7 or 3:4-CH_2<O>C_6H_3·.)

Methylheptenone oxime gives a dihydropyridine by the action of P_2O_5,[4] and on reduction of the product a trimethylpiperidine results. As the δ-carbon atom is fully methylated, a wandering of the double bond must precede ring-closure:

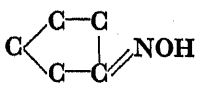


[1] *Ber.*, 1890, **23**, 1795. [2] *Ibid.*, 1895, **28**, 1726.
[3] Scholtz, *ibid.*, 1899, **32**, 1935; Scholtz and Wiedermann, *ibid.*, 1903, **36**, 845; Scholtz and Kepke, *ibid.*, 1904, **37**, 1702; Scholtz and Meyer, *ibid.*, 1910, **43**, 1861. [4] Wallach, *Ann.*, 1899, **309**, 29; 1901, **319**, 77.

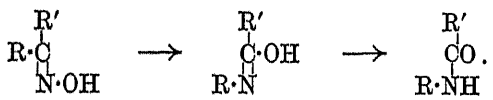
The possibility of a Beckmann transformation (before or after the rearrangement of linkages) is not excluded, and the final product may thus be 2 : 3 : 3-trimethylpiperidine :



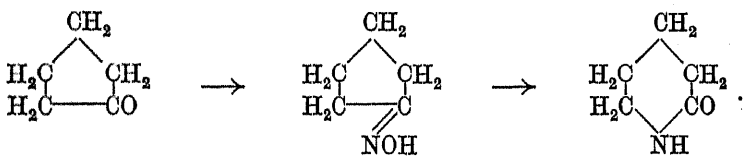
Allylacetone oxime, $CH_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}NOH$, does not give a pyridine derivative under these conditions.

27. From oximes of cyclic ketones : 

The Beckmann change, by which an oxime is converted into an acid amide, may be figured thus :



Now if R and R′ are the two ends of a five-carbon chain, the resulting product will be a piperidone. Wallach [1] has obtained a number of α-piperidones from the oximes of the corresponding *cyclo*-pentanones by the action of PCl_5 or conc. H_2SO_4 :



(65% yield.)

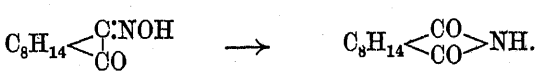
3-Methylpentanone oxime gives the expected isomerides,



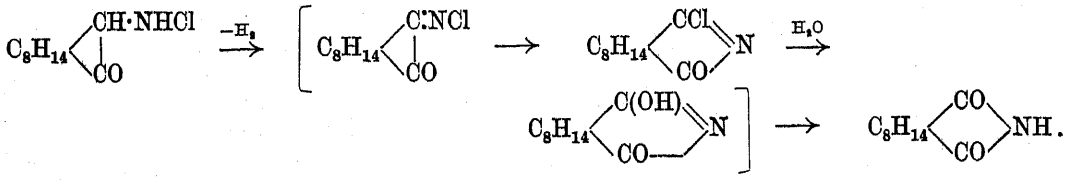
The preparation of camphorimide by the action of conc. H_2SO_4, conc. HCl or the Beckmann

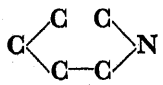
[1] *Ann.*, 1899, **309**, 13; 1900, **312**, 179, 184; 1902, **324**, 285, 288.

mixture (HCl + acetic acid + acetic anhydride) upon *iso*nitrosocamphor or upon *iso*nitroso*epi*-camphor is an example of the same reaction : [1]

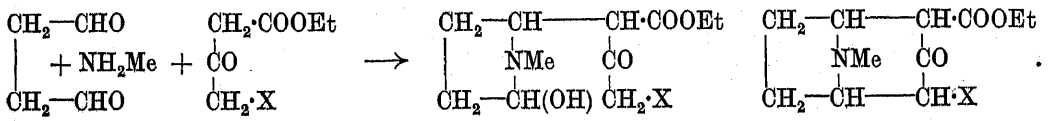


Chlorylaminocamphor yields camphorimide when treated with hot water : [2]



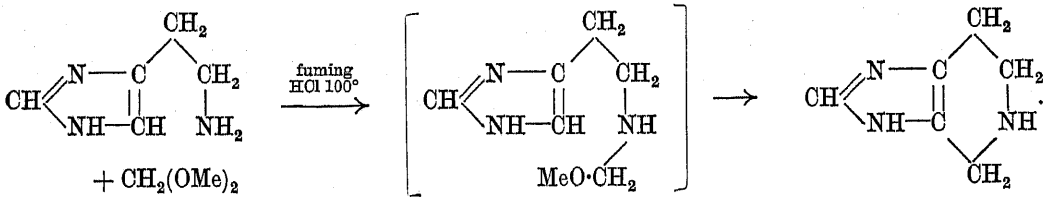
28. By ring-closure in the α : β-position : 

In Robinson's synthesis of tropinone [3] the pyridine ring is closed in the α : β-position :



(X = H, ·COOH or ·COOEt.)

The preparation of methenyl-3 : 4-diamino-1 : 2 : 3 : 6-tetrahydropyridine by the method of Swiss Patent 92297 (1922) also probably involves an α : β-ring-closure, for it is analogous to the *iso*quinoline syntheses described on p. 315 :



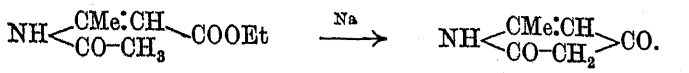
[1] Angeli, *Ber.*, 1893, **26**, 58; Manasse, *ibid.*, p. 241; Claisen and Manasse, *Ann.*, 1893, **274**, 81; Bredt and Perkin, *J. C. S.*, 1913, **103**, 2211.

[2] Forster and Schlaepfer, *ibid.*, 1914, **105**, 2775.

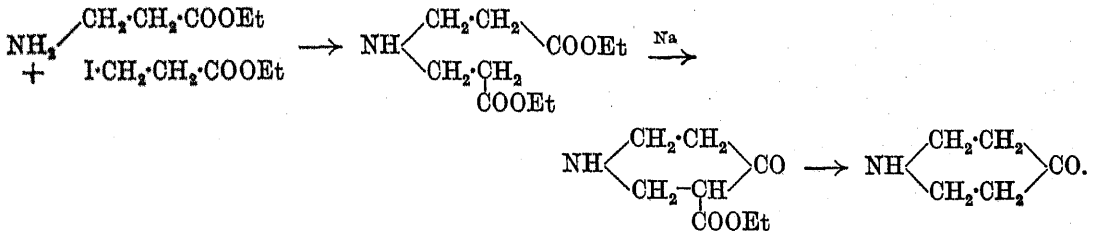
[3] *Ibid.*, 1917, **111**, 762; D.R.-PP. 344031, 345759, 3 689

29. By ring-closure in the $\beta:\gamma$-position : CO<CH$_2$·C / C—C>N

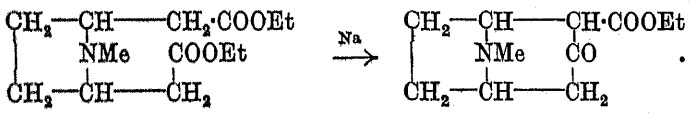
Acetyl-β-aminocrotonic ester is converted into 4 : 6-dihydroxypicoline by the action of sodium in toluene : [1]



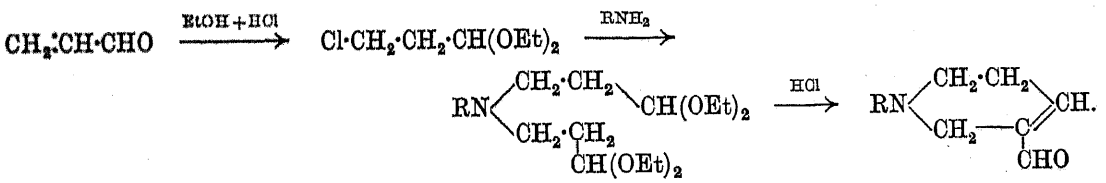
Ruzicka and Fornasir [2] devised the following method for the preparation of the previously unknown γ-piperidone :*



A similar reaction is used in the conversion of 1-methylpyrrolidine-2 : 5-diacetic ester into tropinonecarboxylic ester : [3]

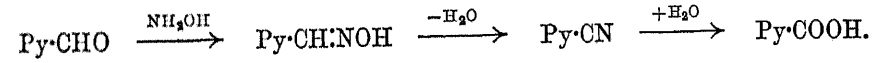


Wohl's syntheses of aldehydotetrahydropyridines from the diacetal of β-iminodipropionaldehyde [4] also involve a $\beta:\gamma$-ring-closure :



(R = H, Me, Et.)

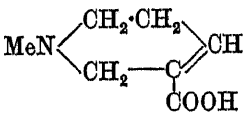
This method has been applied by Wohl and Johnson [5] to the synthesis of arecaidine and arecoline, two alkaloids found in areca nuts. The *N*-methyl derivative prepared as above (R = Me) was converted into the acid without oxidation of the ring hydrogens by the following method :



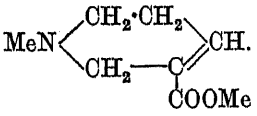
[1] D.R.-P. 102894.
[2] *Helv. Chim. Acta*, 1920, **3**, 806.
[3] D.R.-P. 302401.
[4] *Ber.*, 1905, 38, 4161, 4170; 1907, **40**, 4679, 4685, 4698.
[5] *Ibid.*, p. 4712.

* Other attempts to prepare this compound have been unsuccessful. It cannot be obtained from γ-hydroxypyridine by reduction nor from γ-hydroxypiperidine by oxidation, and Petrenko-Kritschenko's method from acetonedicarboxylic ester fails in the case of formaldehyde (see p. 209).

The acid (arecaidine) was esterified with methyl alcohol to give arecoline :



Arecaidine.

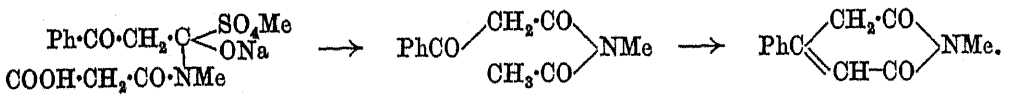


Arecoline.

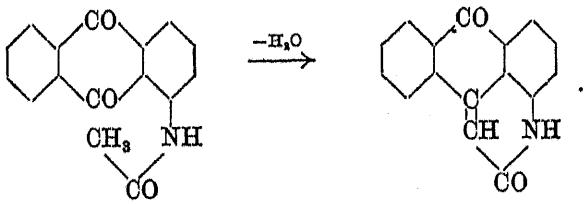
Knust and Mumm [1] have obtained a diketotetrahydropyridine by the action of sodium malonate upon the methosulphate of 5-phenyl*iso*oxazole, which reacts as if it had an open chain structure :



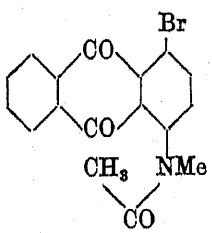
The sodium malonate is added at the C:N linkage :

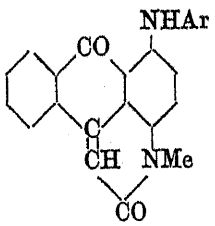


To this group of syntheses belong the " pyridonations " of various α-acetylaminoanthraquinones by the action of hot, very dilute alkali : [2]

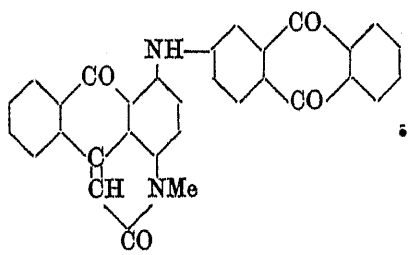


Sodium acetate, alone or mixed with acetic anhydride, also brings about this reaction, which has been extended [3] by the use of malonyl instead of acetyl derivatives. The dyestuffs Alizarine Rubinole B and R and Algol Red B are of the anthrapyridone type, derived from bromo-acetylmethylaminoanthraquinone by " pyridonation " followed by condensation with aniline, toluidine or β-aminoanthraquinone. The Rubinoles are sulphonated.





Alizarine Rubinoles.

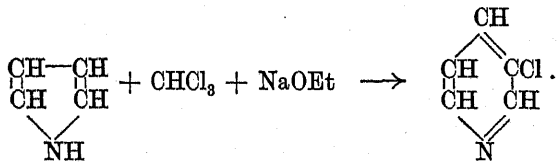


Algol Red B.

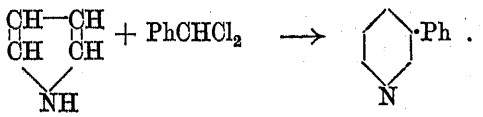
[1] *Ber.*, 1917, **50**, 569. [2] D.R.-PP. 203752, 209033, 212204, 216597. [3] D.R.-P. 250885.

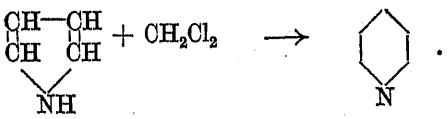
30. From pyrroles

The widening of the pyrrole ring by the action of chloroform and NaOEt was first observed by Ciamician and Dennstedt [1]:



The reaction was extended by Dennstedt and Zimmermann [2] to CCl_4, $PhCHCl_2$ and CH_2Cl_2:

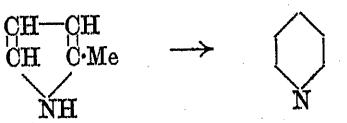




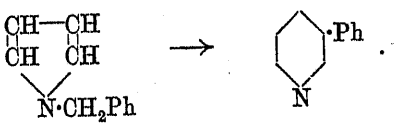
The intermediate, $C_4H_4N{\cdot}CHCl_2$, has not been detected in the reaction products, though the corresponding indole compound (which gives a quinoline derivative) may be isolated.

Dennstedt and Zimmermann [3] also obtained pyridine by heating 1- or 2-methylpyrrole with HCl in a sealed tube.

The same widening of the ring occurs when the methylpyrrole is led through a tube heated to dull redness [4]:

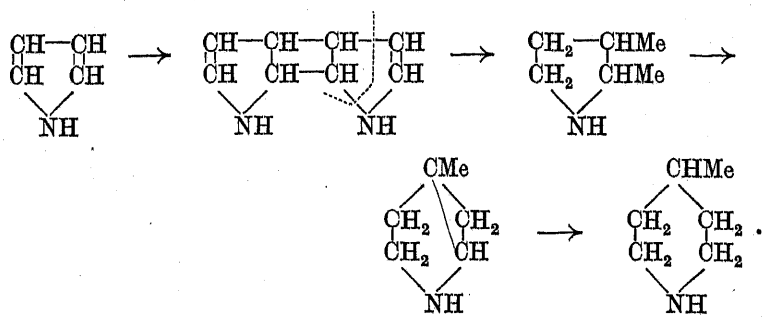


That the additional C atom is here also introduced in the β-position was shown by Pictet,[5] who obtained 17% of β-phenylpyridine from *N*-benzylpyrrole:



[1] *Gazz.*, 1881, **11**, 300; 1882, **12**, 211; *Ber.*, 1881, **14**, 1153; 1882, **15**, 1172; see also Ciamician and Silber, *Gazz.*, 1885, **15**, 186; 1887, **17**, 11; *Ber.*, 1885, **18**, 721; 1887, **20**, 191.
[2] *Ber.*, 1885, **18**, 3316; see also Bocchi, *Gazz.*, 1900, **30**, i, 89.
[3] *Ber.*, 1886, **19**, 2198.
[4] Pictet, *ibid.*, 1904, **37**, 2792; 1905, **38**, 1946.
[5] *Loc. cit.*

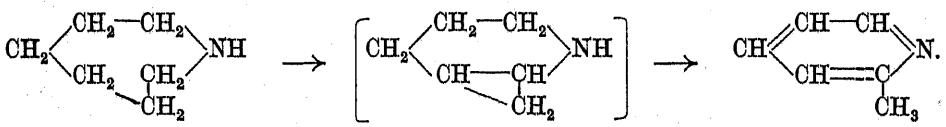
Putochin [1] obtained 4-methylpiperidine by passing pyrrole with hydrogen over nickel at 200°:



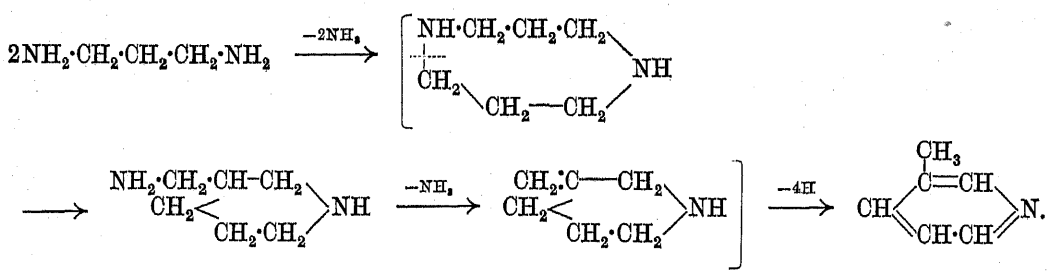
Here again the additional carbon atom takes up the β-position.

31. From seven-membered and higher rings:

Schmidt [2] has recently shown that the oxidation of hexamethyleneimine with silver acetate in 10% acetic acid yields α-picoline:



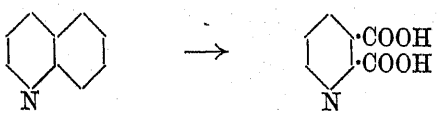
Trimethylenediamine undergoes a peculiar decomposition when the hydrobromide is distilled,[3] β-picoline being formed from the eight-membered ring compound first produced:



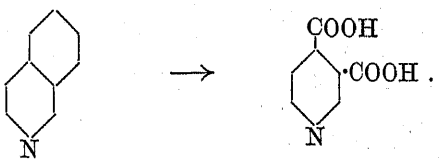
[1] *Ber.*, 1922, **55**, 2742. [2] *Ibid.*, p. 1584. [3] Ladenburg and Sieber, *ibid.*, 1890, **23**, 2727.

32. From quinolines etc.

When quinoline is oxidised with permanganate, pyridine-2 : 3-dicarboxylic acid (quinolinic acid) results,[1] while *iso*quinoline gives cinchomeronic acid [2]:

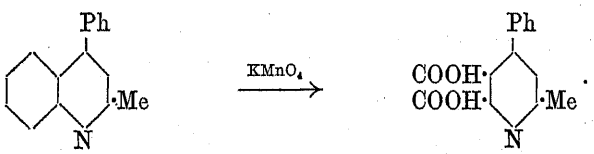


Quinoline. *Quinolinic acid.*



iso*Quinoline.* *Cinchomeronic acid.*

Substitution in the benzene nucleus facilitates the oxidation.[3] Substituent radicals in the pyridine nucleus remain unoxidised.[4] Thus Bülow and Issler [5] obtained 4-phenyl-6-methyl-quinolinic acid from the corresponding quinoline:



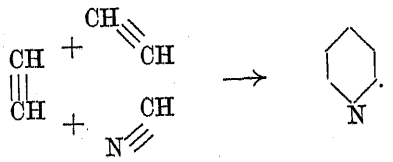
Atophan similarly yields 2-phenylpyridine-4 : 5 : 6-tricarboxylic acid.[6] Späth and Koller [7] oxidised 4-chloroquinoline to the corresponding chloroquinolinic acid required for their synthesis of ricinine.

The dimethyl-β-naphthoquinoline obtained by Reed [8] from paraldehyde, acetone and β-naphthylamine (see p. 262) gives on oxidation a dimethylquinolinic acid. The oxidation of other naphthoquinolines is described by Ciusa.[9]

[1] Koenigs, *Ber.*, 1879, **12**, 983.
[2] Hoogewerff and van Dorp, *Rec. trav. chim.*, 1885, **4**, 285.
[3] Fischer and Renouf, *Ber.*, 1884, **17**, 755.
[4] v. Miller, *ibid.*, 1900, **33**, 2252; 1901, **34**, 1900.
[5] *Ibid.*, 1903, **36**, 3450.
[6] Boehm and Bournot, *ibid.*, 1915, **48**, 1570.
[7] *Ibid.*, 1923, **56**, 2454.
[8] *J. pr. Chem.*, 1887, **35**, 298.
[9] *R. A. L.*, 1914, [v], **23**, ii, 262, 265.

33. Pyrogenous methods :

A small amount of pyridine is formed when acetylene and hydrocyanic acid gas are passed through a hot tube : [1]



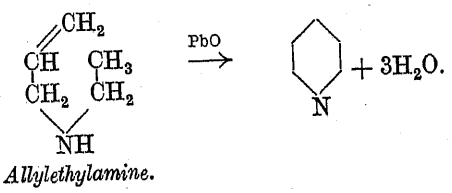
The reaction has been studied by Meyer,[2] who also obtained small quantities of pyridine bases from acetylene and ammonia at 650°.[3] Acetylene, HCN and CH_4, at 650°, gave a mixture of pyridine bases.

Tschitschibabin [4] passed a mixture of acetylene and ammonia over alumina, iron oxide or chromium oxide at 300°. The product contained α- and γ-picolines, several collidines (*e.g.* 2-methyl-3-ethylpyridine) and a little pyrrole, but no pyridine and no lutidines. When Al_2O_3 was used, much aldehyde-ammonia was produced, and at higher temperatures this was converted into aldehyde-collidine and γ-alkylpyridines. A mixture of acetylene, benzaldehyde and ammonia yielded α- and γ-phenylpyridines.

The earliest synthesis of pyridine is that of Chapman,[5] who heated amyl nitrate with P_2O_5 :

$$C_5H_{11}\cdot O\cdot NO \longrightarrow C_5H_5N + H_2 + 2H_2O.$$

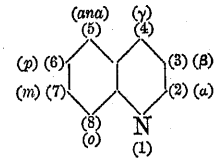
Any five-carbon secondary amine gives a certain amount of pyridine when passed through a hot tube or over hot litharge : [6]



Allylethylamine.

[1] Ramsay, *Jahresber.*, 1877, 436.
[2] *Ber.*, 1912, **45**, 1609; 1913, **46**, 3183.
[3] Meyer and Wesche, *ibid.*, 1917, **50**, 424, 434; D.R.-PP. 369371, 369373.
[4] *Zentr.*, 1916, i, 920.
[5] *J. C. S.*, 1866, **19**, 336; *Ann. Suppl.*, 1868, **6**, 329.
[6] Koenigs, 1879.

CHAPTER VIII

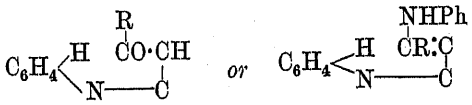
QUINOLINES, 

Introductory:

THE numerous synthetic methods available for the preparation of quinoline derivatives may be grouped as follows, according to the position of the atoms involved in the ring-closure:

I. Ring-closure between γ-carbon atom and the benzene nucleus:

In this group (sects. 1–12), which includes the very important Skraup, Döbner-Miller and Döbner syntheses, an intermediate compound of the type *:



is formed and ring-closure occurs by elimination of water or aniline.

Skraup's method (sect. 1) from an arylamine, glycerol and conc. H_2SO_4 in the presence of an oxidant, is of practically universal applicability and leads to *quinolines* unsubstituted in the hetero-ring.

The Döbner-Miller method (sect. 2) uses aldehydes with arylamines, giving α-substituted *quinolines*—especially *quinaldines*. It may be modified so as to yield *β-methylquinoline*. *Cinchoninic acids*, usually with an α-substituent, are readily obtained by Döbner's method (sect. 3) from arylamines, pyruvic acid and aldehydes. For γ-substituted *quinolines* Beyer's modification (sect. 4) of the Döbner-Miller synthesis may be employed, one of the aldehyde molecules being replaced by acetone or acetophenone. The condensation of arylamines with ketones (sect. 5) gives α : γ-disubstituted *quinolines*.

A reaction of somewhat limited application is the preparation of *β : γ-dicarboxylated* quinolines from oxalacetic ester arylamines and aldehydes (sect. 6). In the absence of the aldehyde an *α-hydroxycinchoninic ester* is formed.

γ-Substituted *quinolines* are obtainable by Blaise and Maire's method (sect. 7).

Acetoacetic ester and similar compounds may be used for the preparation of 4-*hydroxyquinaldines* (sect. 8*a*), 2 : 4-disubstituted *quinolines* (sect. 8*a*) and *carbostyrils* (sect. 8*b*). Malonic ester in the same way yields 2 : 4-*dihydroxy-* or 2 : 4-*dichloro-quinolines* (sect. 9).

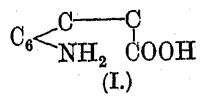
In Just's method (sect. 10) an aromatic imide-chloride is condensed with sodiomalonic ester to give 4-*hydroxyquinoline*-3-*carboxylic esters*.

The julolidine synthesis can be made to give simple *tetrahydroquinolines* (sect. 11) and the method of Spallino and Salimei (sect. 12) leads to a limited number of 2 : 4-disubstituted *quinolines*.

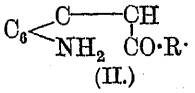
* See Simon, *Compt. rend.*, 1907, **144**, 138.

II. Ring-closure between nitrogen atom and the benzene nucleus:

Most of the syntheses in this group (sects. 13–18) involve the lactamisation of an acid of the type (I) or the anhydrisation of an *o*-amino-ketone (II):



(I.)



(II.)

The *o*-amino-group may also close the ring by addition at an unsaturated linkage. Only rarely is the quinoline ring closed by internal oxidation at the expense of an " ortho-nitro " group (cf. Indoles, p. 91). One such case is the quindoline synthesis of Fichter and Boehringer (p. 276).

The reduction of *o*-nitrocinnamic acids (sect. 13) yields *carbostyrils* or *dihydrocarbostyrils* according to conditions, thus providing an easy synthesis of these compounds from *o*-nitro-aldehydes. The saturated acids give *dihydrocarbostyrils* (sect. 14).

A number of methods for the preparation of 2 : 4-*dihydroxyquinolines* involve the intermediate formation of an *o*-aminobenzoylacetic ester (sect. 15).

The replacement of the acid group in the foregoing syntheses by a ketonic group leads to *tetrahydroquinolines*, *quinolines* or 4-*hydroxyquinolines* (sect. 16).

Ring-closure by addition of an *ortho*-NH_2 group at a suitably placed ethylene linkage (sect. 17) or $\cdot C{\equiv}N$ (sect. 18) gives *α-acetonylquinoline* or *α-aminoquinolines*.

III. Ring-closure between β- and γ-carbon atoms:

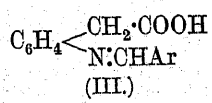
This group (sects. 19–25) includes three important general methods—those of Friedländer, Pfitzinger and v. Niementowski from *o*-amino-aldehydes, *o*-aminobenzoylformic acid and *o*-aminobenzoic acid respectively. Friedländer's method (sect. 19) gives *quinolines*, while Pfitzinger's (sect. 20) leads to *cinchoninic acids*. Both are especially suitable for the preparation of quinolines with α- or β-substituents. The ketones used in these syntheses may be replaced by " dinitriles " (sect. 21) with formation of *β-cyanoquinolines*. v. Niementowski's method (sect. 22) for 4-*hydroxyquinolines* from anthranilic acids is less general than these, as there is a tendency to give the Döbner-Miller product.

The cyclisation of acyl-*o*-aminoketones (sect. 23) may occur in two ways, giving 2- or 4-*hydroxyquinolines*, according as the ketonic or the acyl carbonyl group takes part.

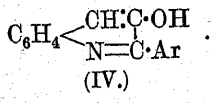
The *Flavaniline* synthesis (sect. 24) is a special method scarcely capable of generalisation. Kulisch's glyoxal method (sect. 25) for *quinolines* recalls Hinsberg's indole synthesis (p. 112), but is more direct.

IV. Ring-closure between α- and β-carbon atoms:

A few cases of this type of quinoline synthesis are known (sect. 26); they are interesting rather than important. The supposed conversion of benzal-*o*-aminophenylacetic acids (III) into β-hydroxy-α-arylquinolines (IV) [1] has been shown to give, not quinolines, but oxindoles.[2]



(III.)



(IV.)

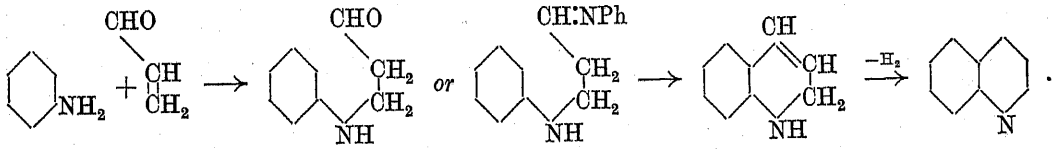
[1] Neber, *Ber.*, 1922, **55**, 838.
[2] Kliegl and Schmalenbach, *ibid.*, 1923, **56**, 1517; Neber and Röcker, *ibid.*, p. 1710; see p. 132.

There remain to be mentioned the Bz-*tetrahydrocarbostyrils* prepared by Sen Gupta (sect. 27) and the *dihydrocarbostyrils* obtained from hydrindone oximes (sect. 28), the formation of *quinolines* by widening of the indole ring (sect. 29) and of *quinolinecarboxylic acids* by oxidation of acridines, etc. (sect. 30), Knoevenagel and Fries' remarkable *trihydroxyquinaldine* synthesis in which both rings are built up from chain compounds (sect. 31) and finally the pyrogenous synthesis of *quinolines* (sect. 32).

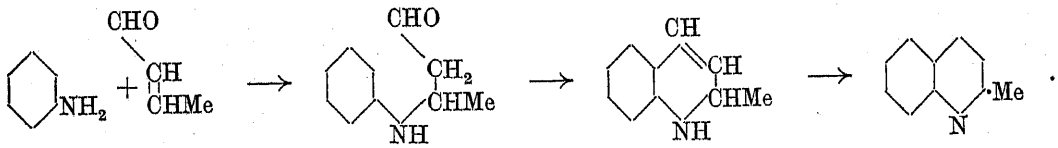
1. Skraup's reaction: $C_6{<}^{CHO\cdot CH}_{N\text{—}C}$

This important and very general synthetic method consists in heating together an aromatic amine, glycerol and conc. H_2SO_4 with the addition of an oxidising agent. Skraup [1] originally used nitrobenzene (or the nitro compound corresponding to the amine) as oxidant, but Knüppel [2] obtained better yields in many cases by the employment of As_2O_5. The nitroanilines in particular give only small yields by the ordinary Skraup reaction, but 60–80% by Knüppel's method. Picric acid is also useful in the case of nitro- and dinitro-anilines.[3] Calcined ferric oxide with aniline, glycerol and H_2SO_4 gives quinoline in 60% yield.[4]

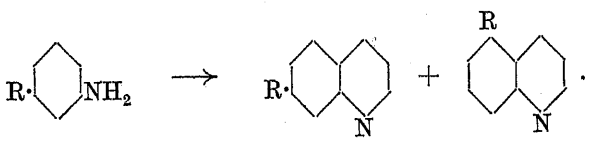
The mechanism of the Skraup reaction seems to be as follows [5]: The glycerol is converted by the H_2SO_4 into acroleïn, which then condenses with the base and the ring is closed by dehydration (or loss of aniline):



Crotonaldehyde with aniline and H_2SO_4 gives quinaldine, not lepidine.[6] Skraup's original suggestion that a Schiff base is first formed is thus excluded [7]:

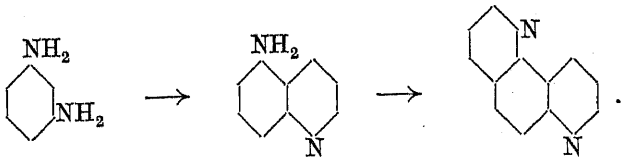


Meta substituted arylamines in which both *ortho* positions are free can give two isomeric quinolines:



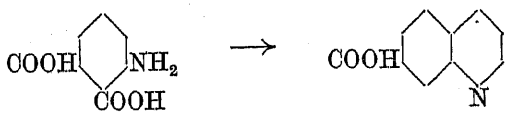
[1] *Ber.*, 1880, **13**, 2086; 1882, **15**, 897.
[2] *Ibid.*, 1896, **29**, 703.
[3] Kaufmann and Hüssy, *ibid.*, 1908, **41**, 1739.
[4] de Barry Barnett, *Chem. News*, 1920, **121**, 205.
[5] Simon, *Compt. rend.*, 1907, **144**, 138.
[6] Blaise and Maire, *ibid.*, p. 93.
[7] Cf. v. Miller, *Ber.*, 1891, **24**, 1720.

The 5- (*i. e.* the *ana*-) isomer usually predominates,[1] but further investigation seems desirable. From *m*-phenylenediamine is obtained phenanthroline, which is a 5-derivative [2]:

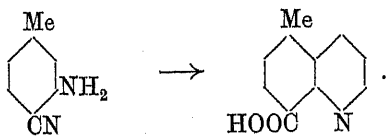


Phenanthroline.

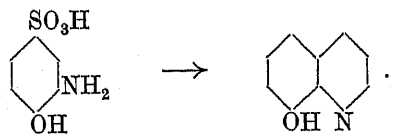
m-Nitroaniline by Knüppel's method gives a mixture of 5- and 7-nitroquinolines in the proportion 4 : 1.[3] On the other hand, *m*-aminobenzoic acid yields mainly quinoline-7-carboxylic acid.[4] The same acid results when 3-aminophthalic acid is submitted to the Skraup reaction, the 8-carboxyl group being eliminated [5]:



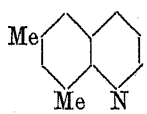
This reactivity of the 8-position during the Skraup reaction is also shown in the case of 4-cyano-*m*-toluidine, the ·CN being hydrolysed to ·COOH [6]:



Aminophenolsulphonic acids lose the sulphonic group and give hydroxyquinolines [7]:



Ewins [8] showed that the Skraup product from 4-*m*-xylidine, viz.:



[1] See Rist, *Ber.*, 1890, **23**, 3483; Decker and Remfry, *ibid.*, 1905, **38**, 2773.
[2] Skraup, *ibid.*, 1882, **15**, 893, etc.
[3] Decker, *J. pr. Chem.*, 1901, **63**, 576.
[4] Skraup, *Ber.*, 1882, **15**, 893; Lellmann and Alt, *Ann.*, 1887, **237**, 307.
[5] Tortelli, *R. A. L.*, 1886, [iv], **2**, 523.
[6] v. Jakubowski, *Ber.*, 1910, **43**, 3028.
[7] Claus, *J. pr. Chem.*, 1890, **41**, 32.
[8] *J. C. S.*, 1913, **103**, 102.

was identical with β-cytisolidine, a reduction product of cytisine, an alkaloid isolated by Freund in 1904 from *Cytisus laburnum*. α-Cytisolidine is the corresponding tetrahydrodimethylquinoline.[1]

The Skraup reaction fails with *p*-aminoacetophenone,* but goes easily with *p*-aminobenzophenone.

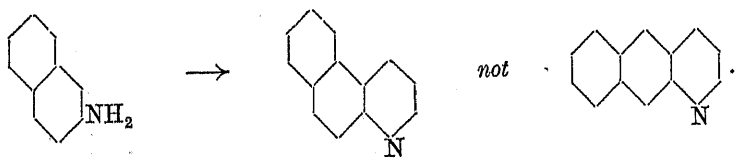
As has been mentioned, *m*-phenylenediamine undergoes a double Skraup reaction. Benzidine similarly gives 6 : 6′-diquinolinyl : [2]



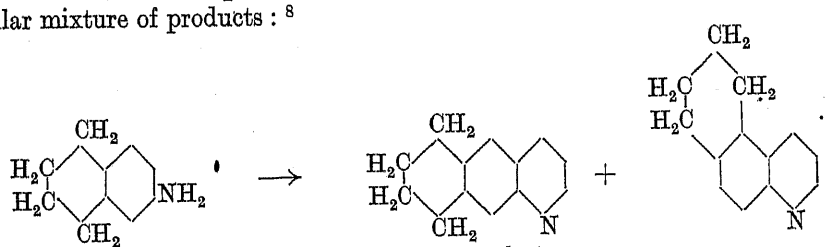
Claus and Stegelitz,[3] attempting to substitute azobenzene for the mixture of nitrobenzene and aniline in the Skraup reaction, obtained the same product. The azobenzene is reduced to hydrazobenzene, which at once isomerises to benzidine. Lellmann and Lippert [4] later succeeded in obtaining small yields of quinoline and 6-methylquinoline from azobenzene and *p*-azotoluene respectively.

Only minute traces of quinoline result when phenylhydroxylamine is heated with glycerol and H_2SO_4.[5]

β-Naphthylamine by the Skraup reaction yields only one naphthoquinoline, viz. the "angular" isomer. So great indeed is the tendency for ring-closure in the α-position that an α-Br or α-NO_2 is eliminated : [6]

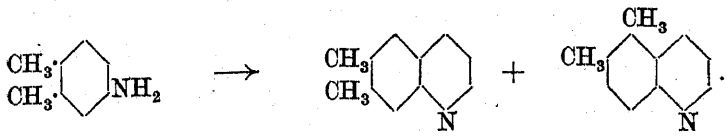


ar-Tetrahydro-β-naphthylamine, on the other hand, gives, in 65% yield, a mixture of the two isomers, in which the *linear* compound predominates.[7] The analogously constituted 4-*o*-xylidine gives a similar mixture of products : [8]



Main product.

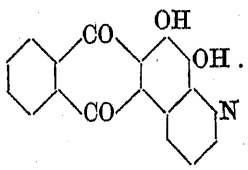
[1] Berend and Thomas, *Ber.*, 1892, **25**, 2548.
[2] Roser, *ibid.*, 1884, **17**, 1817, 2767; Ostermayer and Henrichsen, *ibid.*, p. 2444.
[3] *Ibid.*, p. 2380.
[4] *Ibid.*, 1891, **24**, 2623.
[5] Bamberger and Weitnauer, *ibid.*, 1922, **55**, 3377.
[6] Lellmann and Schmidt, *ibid.*, 1887, **20**, 3154; v. Braun and Gruber, *ibid.*, 1922, **55**, 1710.
[7] Lellmann and Schmidt, *loc. cit.*
[8] Berend, *Ber.*, 1884, **17**, 1489; Lellmann and Schmidt, *loc. cit.*
* A quinaldine is obtainable by Döbner and v. Miller's method, but the yield is small.



Main product.

Here, as will be seen, the 7-isomer predominates.

In the anthracene series the quinoline from β-aminoalizarine has long been known. Prud'homme [1] heated β-nitroalizarine with glycerol and H_2SO_4; the blue product was shown by Graebe [2] to be the corresponding quinoline:



α-Aminoalizarine gives a green dyestuff by the usual Skraup reaction. Other anthraquinolines have been similarly prepared.

The following amines have been converted into quinolines by the Skraup reaction:

Amine.	*References.*
Aniline.	3, 4, 7, 8, 13, 82, 86, 122, 123, 124, 125
o-Chloroaniline.	78
m-Chloroaniline.	26, 39
p-Chloroaniline.	12, 13, 45
o-Bromoaniline.	53, 79
m-Bromoaniline.	53, 63
p-Bromoaniline.	12, 53
o-Nitroaniline.	15, 86
m-Nitroaniline.	15, 55, 86, 93, 94
p-Nitroaniline.	15, 86, 94.
Metanilic acid.	51
Sulphanilic acid.	19, 22, 86
m-Aminodimethylaniline.	86
p-Aminodimethylaniline.	15, 86, 126
p-Aminodiethylaniline.	126
p-Aminoacetophenone.	77 (fails).
2 : 4-Dichloroaniline.	12
2 : 5-Dichloroaniline.	12
3 : 5-Dichloroaniline.	84
2 : 5-Dibromoaniline.	21
3 : 4-Dibromoaniline.	62
3 : 5-Dibromoaniline.	62
2 : 3- / 3 : 4- / 3 : 5- Dinitroanilines.	105
2-Bromoaniline-5-sulphonic acid.	54
Phenylhydroxylamine.	131 (fails)
o-Toluidine.	7, 13, 86, 97, 122, 134
m-Toluidine.	9, 13, 42, 122, 134

[1] *Bull. Soc. chim.*, 1877, [ii], **28**, 62.

[2] *Ann.*, 1880, **201**, 335.

Amine.	*References.*
p-Toluidine.	7, 13, 70, 98, 122
5-Bromo-*o*-toluidine.	64
4-Chloro-*m*-toluidine.	37, 135
4-Nitro-*o*-toluidine.	73
2-Nitro-*p*-toluidine.	70, 114
3-Nitro-*p*-toluidine.	70, 98
o-Toluidine-4-sulphonic acid.	19, 25, 73
o-Toluidine-5-sulphonic acid.	25
p-Toluidine-2-sulphonic acid.	111
p-Toluidine-3-sulphonic acid.	19, 23
2 : 6-Diaminotoluene-4-sulphonic acid.	80
4-Cyano-*m*-toluidine.	113
4-*o*-Xylidine.	27, 132
4-*m*-Xylidine.	31, 70, 116, 123
p-Xylidine.	38, 40, 56
6-Nitro-4-*m*-xylidine.	70
2-*p*-Xylidine-6-sulphonic acid.	41, 58
2 : 5-Diamino-*p*-xylene.	68
ψ-Cumidine.	32, 92
4-Amino-3-methyl-1-ethylbenzene.	128
o-Aminopropylbenzene.	119
o-, *m*-, *p*-Aminophenols.	5, 10, 13
o-Anisidine.	10, 117
p-Anisidine.	10, 20, 35
p-Phenetidine.	85, 129
4-Nitro-*o*-anisidine.	95
3-Amino-*o*-cresol.	70
3-Amino-*p*-cresol.	70
4-Amino-1 : 2-dimethoxybenzene.	129
4-Amino-1 : 2-methylenedioxybenzene.	129
Anthranilic acid.	6, 13
m-Aminobenzoic acid.	6, 13, 42, 56
p-Aminobenzoic acid.	6, 13
4-Bromo-3-aminobenzoic acid.	56
3 : 5-Diamino-4-methylbenzoic acid.	80
3 : 4-Dimethoxy-5-aminobenzoic acid.	49 (loses CO_2)
3-Amino-4-hydroxybenzoic acid.	118
4-Amino-3-hydroxybenzoic acid.	118
3-Aminophthalic acid.	46, 48 (loses CO_2)
3-Aminoterephthalic acid.	42
o-Aminodiphenyl.	33
p-Aminodiphenyl.	12, 33
p-Aminotriphenylmethane.	43
α-Naphthylamine.	7, 13, 17, 74, 89, 108
β-Naphthylamine.	13, 17, 57, 75, 81, 86, 88, 104, 132
ar-Tetrahydro-β-naphthylamine.	132
1-Bromo-2-naphthylamine (Br eliminated).	57
1-Nitro-2-naphthalymine (NO_2) ,,	57
1 : 4-Naphthylaminesulphonic acid.	16, 19
2 : 8-Naphthylaminesulphonic acid.	65
2 : 8 : 6-Aminonaphtholsulphonic acid (γ-acid).	87
1-Aminoacenaphthene.	121
β-Aminoanthracene.	24, 81, 86
α-Aminoanthraquinone.	14, 101
β-Aminoanthraquinone.	2, 81, 100, 101, 103
1 : 5(8)-Aminoanthraquinonesulphonic acid.	96
α-Aminoalizarine.	76, 86
β-Aminoalizarine.	1, 2, 71, 81, 86
β-Aminoalizarinesulphonic acid.	59
α- and β-Aminoflavopurpurines.	66
α- and β-Aminoanthrapurpurines.	66

Amine.	*References.*
β-Amino-Alizarine-Bordeaux.	67
1 : 5-Diaminoanthraquinone.	101
9-Aminophenanthrene	106
2-Aminophenanthraquinone.	106
(Dinitroxanthone.)	127
6-Aminoquinoline.	110
8-Aminoquinolone.	60
4-Aminoquinaldine.	80, 83
5-Aminoquinaldine.	60
5-Amino-8-methylquinoline.	70
7-Amino-8-methylquinoline.	80 (fails)
6-Aminokairoline.	130 (fails)
5(7)-Amino-2 : 4-dimethylquinoline.	80
Flavaniline.	44
2-(*m*-Aminophenyl)-quinoline.	36
2- and 4-(*p*-Aminophenyl)-quinolines.	50
2(-*m*-Aminophenyl)-6-methoxyquinoline.	52
2-(*p*-Aminostyryl)-quinoline.	61
Dehydrothiotoluidine.	133
6-Amino-2-*p*-tolyl-aziminobenzene.	90
2-(*o*-Aminophenyl)-benziminazole.	91
2-(*m*-Aminophenyl)-benziminazole.	91
2-(*p*-Aminophenyl)-benziminazole.	91

Double Skraup reactions * have been carried out with the following diamines :

m-Phenylenediamine.	11, 13, 86
p-Phenylenediamine.	13, 18, 110
Benzidine.	28, 29, 30
Benzidinedisulphonic acid.	30
4 : 4′-Dihydroxy-2 : 2′-diaminodiphenyl.	120
Dianisidine.	47
2 : 2′-Diaminodiphenyl.	102
2 : 2′-Diamino-*p*-ditolyl.	102
2 : 4′-Diaminodiphenyl (diphenyline).	34
2 : 2′-Diaminodiphenyl-4 : 4′-dicarboxylic acid.	107
4 : 4′-Diaminobenzophenone.	72
4 : 4′-Diaminodiphenylmethane.	112
4 : 4′-Diaminodiphenylethane.	69
1 : 5-Diaminonaphthalene.	109
1 : 4-Diaminonaphthalene.	80
1 : 5-Diaminoanthraquinone.	101
2 : 6(7)-Diaminoanthraquinones (to benzanthrone quinolines).	100
1 : 5(8)-Diamino-2-methylanthraquinones.	115

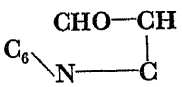
References.

[1] Prud'homme, *Bull. Soc. chim.*, 1877, [ii], **28**, 62. [2] Graebe, *Ber.*, 1878, **11**, 522, 1646; 1879, **12**, 1416; *Ann.*, 1880, **201**, 335, 349. [3] Skraup, *Wien Akad. Ber.*, 1880, **81**, ii, 593; *ibid.*, **13**, 2086. [4] Koenigs, *ibid.*, p. 911. [5] D.R.-P. 14976. [6] Schlosser and Skraup, *Monatsh.*, 1881, **2**, 518. [7] Skraup, *ibid.*, p. 139; *Ber.*, 1881, **14**, 1002. [8] A.P. 241738/1881. [9] Skraup, *ibid.*, 1882, **3**, 381. [10] *Idem*, *ibid.*, p. 531. [11] Skraup and Vortmann, *Monatsh.*, 1882, **3**, 570. [12] La Coste, *Ber.*, 1882, **15**, 557. [13] Skraup, *ibid.*, p. 893. [14] D.R.-P. 26197/1883. [15] La Coste, *Ber.*, 1883, **16**, 669. [16] D.R.-P. 26430. [17] Skraup and Cobenzl, *Monatsh.*, 1883, **4**, 436. [18] Skraup and Vortmann, *ibid.*, p. 569. [19] D.R.-PP. 26430, 29123. [20] D.R.-P. 28324. [21] Metzger, *Ber.*, 1884, **17**, 186. [22] Happ, *ibid.*, p. 191. [23] O. Fischer and Willmack, *ibid.*, p. 440. [24] Graebe, *ibid.*, p. 170. [25] Herzfeld, *ibid.*, pp. 903, 1550. [26] La Coste and Bodewig, *ibid.*, p. 926. [27] Berend, *ibid.*, p. 1489. [28] Roser, *ibid.*, pp. 1817, 2767. [29] Claus and Stegelitz, *ibid.*, p. 2380. [30] Ostermayer and Henrichsen, *ibid.*, p. 2444. [31] Berend, *ibid.*, p. 2716. [32] *Idem*, *ibid.*, 1885, **18**, 376. [33] La Coste and Sorger, *Ann.*, 1885, **230**, 8, 38. [34] O. Fischer, *Monatsh.*, 1885, **6**, 546.

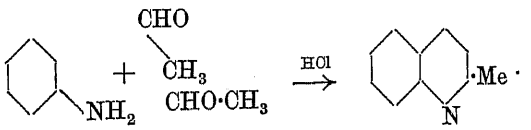
* Complex quinolines have also been obtained from pararosaniline by Noelting and Schwarz (*Ber.*, 1891, **24**, 1606), and from *symm*-triaminobenzene by Pictet and Barbier, *Bull. Soc. chim.*, 1895, [iii], **13**, 29.

[35] Skraup, *ibid.*, p. 760. [36] v. Miller and Kinkelin, *Ber.*, 1885, **18**, 1911. [37] Gattermann and Kaiser, *ibid.*, p. 2602. [38] L. Meyer, *ibid.*, p. 2902. [39] La Coste, *ibid.*, p. 2940. [40] Berend, *ibid.*, p. 3165. [41] Noelting and Kohn, *ibid.*, 1886, **19**, 144. [42] Skraup and Brönner, *Monatsh.*, 1886, **7**, 139, 519. [43] O. Fischer and Fränkel, *Ber.*, 1886, **19**, 749. [44] O. Fischer, *ibid.*, p. 1036. [45] Bornemann, *ibid.*, p. 2377. [46] Tortelli, *R. A. L.*, 1886, iv, **2**, 523. [47] D.R.-P. 38790. [48] Tortelli, *Gazz.*, 1887, **16**, 366. [49] Goldschmiedt, *Monatsh.*, 1887, **8**, 342. [50] Koenigs and Nef, *Ber.*, 1887, **20**, 632. [51] Lellmann and Lange, *ibid.*, p. 1446. [52] v. Miller and Kinkelin, *ibid.*, p. 1924. [53] Claus and Tornier, *ibid.*, p. 2872. [54] Lellmann and Lange, *ibid.*, p. 3084. [55] Claus and Stiebel, *ibid.*, p. 3095. [56] Lellmann and Alt, *Ann.*, 1887, **237**, 307. [57] Lellmann and Schmidt, *Ber.*, 1887, **20**, 3154. [58] Noelting and Frühling, *ibid.*, 1888, **21**, 3156. [59] D.R.-PP. 50164, 50708. [60] Gerdeissen, *Ber.*, 1889, **22**, 244. [61] Bulach, *ibid.*, p. 285. [62] Claus and Geisler, *J. pr. Chem.*, 1889, **40**, 375. [63] Claus and Vis, *ibid.*, p. 382. [64] Alt, *Ann.*, 1889, **252**, 322. [65] Immerheiser, *Ber.*, 1889, **22**, 404. [66] D.R.-PP. 54624, 70665. [67] D.R.-P. 58480. [68] Marckwald, *Ber.*, 1890, **23**, 1015. [69] Comey, *ibid.*, p. 1115. [70] Noelting and Trautmann, *ibid.*, p. 3654; *Bull. Mulhouse*, 1891, 285. [71] D.R.-P. 62703. [72] Noelting and Schwarz, *Ber.*, 1891, **24**, 1606. [73] Lellmann and Ziemssen, *ibid.*, p. 2116. [74] Bamberger and Stettenheimer, *ibid.*, p. 2472. [75] Bamberger and Müller, *ibid.*, p. 2641. [76] D.R.-P. 67470. [77] Berend and Thomas, *Ber.*, 1892, **25**, 2548. [78] Claus and Schöller, *J. pr. Chem.*, 1893, **48**, 140. [79] Claus and Howitz, *ibid.*, p. 151. [80] Marckwald and Schmidt, *Ann.*, 1893, **274**, 352, 356, 361, 364, 373, 376. [81] D.R.-P. 87334. [82] Walter, *J. pr. Chem.*, 1894, **49**, 549. [83] Marckwald, *Ann.*, 1894, **279**, 20. [84] Claus and Ammelberg, *J. pr. Chem.*, 1895, **51**, 415. [85] Grimaux, *Compt. rend.*, 1895, **121**, 749. [86] Knüppel, *Ber.*, 1896, **29**, 703. [87] D.R.-P. 102157. [88] Claus and Besseler, *J. pr. Chem.*, 1898, **57**, 49. [89] Claus and Imhoff, *ibid.*, p. 68. [90] Willgerodt and Dauner, *ibid.*, 1899, **60**, 72. [91] v. Niementowski, *Ber.*, 1899, **32**, 1490; Miklaszewski and v. Niementowski, *ibid.*, 1901, **34**, 2971. [92] Wikander, *ibid.*, 1900, **33**, 646. [93] Decker, *J. pr. Chem.*, 1901, **63**, 573. [94] *Idem*, *ibid.*, **64**, 85. [95] Freyss and Paira, *Bull. Mulhouse*, 1902, **72**, 239. [96] D.R.-P. 149781. [97] Freund, *Ber.*, 1904, **37**, 22. [98] Bartow and McCollum, *J. A. C. S.*, 1904, **26**, 700. [99] Margosches, *J. pr. Chem.*, 1904, **70**, 129. [100] D.R.-P. 171939. [101] D.R.-P. 189234. [102] v. Niementowski and Siefert, *Ber.*, 1905, **38**, 762; *Anz. Akad. Wiss. Krakov*, 1905, 168. [103] Bally, *Ber.*, 1905, **38**, 194. [104] Hepner, *Monatsh.*, 1906, **27**, 1045. [105] Kaufmann and Hüssy, *Ber.*, 1908, **41**, 1735. [106] Herschmann, *ibid.*, p. 1998. [107] v. Jakubowski and v. Niementowski, *ibid.*, 1909, **42**, 634; *Anz. Akad. Wiss. Krakov*, 1909, 219. [108] Haid, *Monatsh.*, 1906, **27**, 315. [109] Finger and Spitz, *J. pr. Chem.*, 1909, **79**, 445. [110] Kaufmann and Radoševic, *Ber.*, 1909, **42**, 2612. [111] Edinger and Bühler, *ibid.*, p. 4313. [112] Borsche and Kienitz, *ibid.*, 1910, **43**, 2333. [113] v. Jakubowski, *ibid.*, p. 3026; *Anz. Akad. Wiss. Krakov*, 1910, A, 598. [114] Bogert and Fischer, *J. A. C. S.*, 1912, **34**, 1569. [115] Schaarschmidt and Stahlschmidt, *Ber.*, 1912, **45**, 3452. [116] Ewins, *J. C. S.*, 1913, **103**, 97. [117] Fränkel and Grauer, *Ber.*, 1913, **46**, 2551. [118] v. Niementowski and Sucharda, *ibid.*, 1916, **49**, 12. [119] v. Braun, Heider and Wyczatkowska, *ibid.*, 1918, **51**, 1223. [120] Bratz and v. Niementowski, *ibid.*, 1919, **52**, 193. [121] Zinke and Raith, *Monatsh.*, 1919, **40**, 271. [122] Druce, *Chem. News*, 1918, **117**, 346; 1919, **119**, 271. [123] Mikeska, Stewart and Wise, *J. Ind. Eng. Chem.*, 1919, **11**, 456. [124] de Barry Barnett, *Chem. News*, 1920, **121**, 205. [125] Druce, *ibid.*, p. 239. [126] Barbier, *Bull. Soc. chim.*, 1920, [vi], **27**, 427. [127] Dar, *J. C. S.*, 1920, **117**, 1053. [128] Mailhe, *Compt. rend.*, 1921, **173**, 160. [129] Sonn and Benirschke, *Ber.*, 1921, **54**, 1730. [130] Lindner, *Monatsh.*, 1922, **42**, 421. [131] Bamberger and Weitnauer, *Ber.*, 1922, **55**, 3377. [132] v. Braun and Gruber, *ibid.*, p. 1710. [133] Bogert and Meyer, *J. A. C. S.*, 1922, **44**, 1572; *Chem. News*, 1922, **124**, 319. [134] v. Braun, Gmelin and Schultheiss, *Ber.*, 1923, **56**, 1341. [135] v. Braun and Kühlein, *ibid.*, p. 1351.

2. Döbner and v. Miller's reaction :

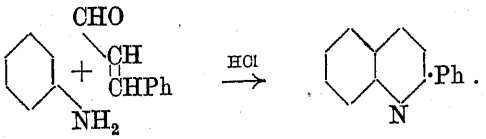


Döbner and v. Miller [1] in 1881 substituted "ethylene alcohol" (*i.e.* glycol) for glycerol in the Skraup reaction and obtained quinaldine. This result they attributed to the conversion of the glycol into acetaldehyde, and in accordance with this they discovered that paraldehyde heated with aniline and H_2SO_4 (or, better, with conc. HCl) gave quinaldine :

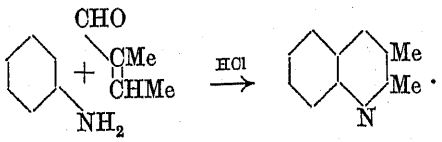


[1] *Ber.*, 1881, **14**, 2812.

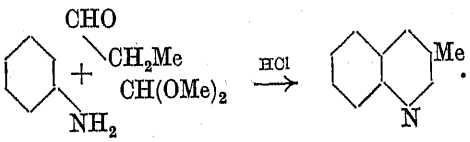
From aniline and cinnamaldehyde [1] they obtained 2-phenylquinoline :



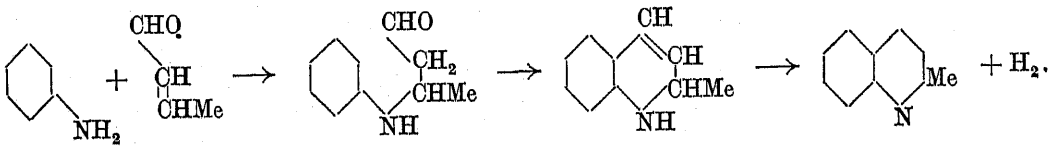
Later work showed that practically any aromatic amine may be condensed (i) with an unsaturated aldehyde, or (ii) with two molecules of an aldehyde $R{\cdot}CH_2{\cdot}CHO$, or (iii) with one molecule of $R{\cdot}CH_2{\cdot}CHO$ and one molecule of $R'{\cdot}CHO$, to give substituted quinolines. For example, aniline and tiglic aldehyde give 2 : 3-dimethylquinoline : [2]



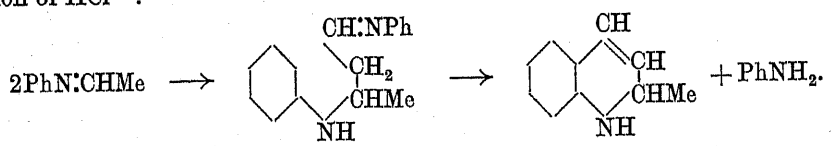
3-Methylquinoline results from the condensation of aniline, propionaldehyde and methylal : [3]



The mechanism of the reaction was first satisfactorily explained by C. Beyer,[4] who suggested that crotonaldehyde, produced from two molecules of paraldehyde, formed an additive product with the aniline, ring-closure then proceeding as in the Skraup reaction [5] :

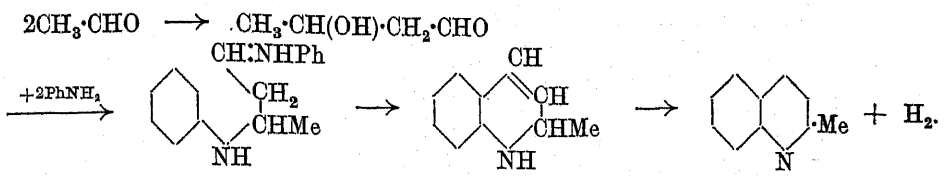


v. Miller obtained dihydroquinaldine in 22% yield from Eckstein's dimeric ethylidene-aniline by the action of HCl * :

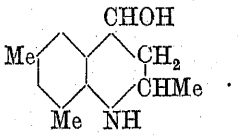


[1] *Ber.*, 1883, **16**, 1605. [2] v. Miller, *ibid.*, 1887, **20**, 1912; Rohde, *ibid.*, 1889, **22**, 267.
[3] v. Miller and Kinkelin, *ibid.*, 1887, **20**, 1916. [4] *J. pr. Chem.*, 1886, **33**, 423. [5] *Ber.*, 1892, **25**, 2072.
* In the presence of benzaldehyde the aniline formed is converted into benzalaniline, which removes hydrogen from the dihydroquinaldine. The products are benzylaniline and benzalquinaldine (Eibner, *Ann.*, 1901, **318**, 58). Eckstein's base is a *trans* compound and distils unchanged. The *cis* isomer, prepared by Eibner, yields quinaldine when distilled.

This reaction seems to favour Bischler's explanation [1]:



Further light was thrown upon the subject by Jones and his collaborators.[2] No hydrogen is actually liberated during the reaction, and Jones considered that the dihydroquinaldine was at once converted into a mixture of quinaldine and tetrahydroquinaldine. The "aldol bases" obtained by Miller and Plöchl [3] from 4-*m*-xylidine and acetaldehyde were shown to be *cis* and *trans* forms of the compound



Similar *cis* and *trans* aldol bases were obtained from *p*-toluidine and *ψ*-cumidine. All were converted by heat or by mineral acid into the corresponding dihydroquinolines, which at once gave mixtures of the quinoline and its tetrahydro-derivative.

Finally, Mills, Harris and Lambourne [4] have shown that the hydrogen available in the Döbner–v. Miller synthesis is utilised, not in the formation of tetrahydroquinaldine, but in the reduction of Schiff bases formed as by-products. In the case of aniline and acetaldehyde, the products are quinaldine, ethylaniline and butylaniline,* the two latter being derived from PhN:CHMe and PhN:CH·CH:CHMe.

Incidentally Mills, Harris and Lambourne found that the addition of a little $ZnCl_2$ led to increased yields.

As in the Skraup reaction, *m*-substituted anilines give both 5- and 7-substituted quinolines. Rist [5] obtained always the 7-derivative by the Döbner–v. Miller reaction and the 5-isomeride by Skraup's method. Decker and Remfry,[6] on the other hand, conclude that the 5-derivative is formed in both cases as main product.

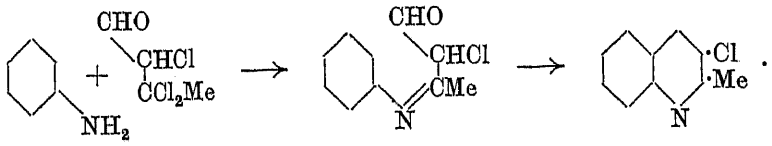
Certain variants of the Skraup and Döbner–v. Miller syntheses may be mentioned here. Wallach and Wüsten [7] obtained quinaldine from aniline, lactic acid, nitrobenzene and conc. H_2SO_4. The lactic acid is evidently first converted into acetaldehyde [8]:

$$CH_3\cdot CH(OH)\cdot COOH \longrightarrow CH_3\cdot CHO + H_2O + CO.$$

[1] *Ber.*, 1892, **25**, 2864.
[2] *J. C. S.*, 1911, **99**, 334; 1912, **101**, 1376, 1389; see also Blaise and Maire, *Bull. Soc. chim.*, 1908, [iv], **3**, 658.
[3] *Ber.*, 1896, **29**, 1462.
[4] *J. C. S.*, 1922, **119**, 1294.
[5] *Ber.*, 1890, **23**, 3483.
[6] *Ibid.*, 1905, **38**, 2773.
[7] *Ibid.*, 1883, **16**, 2007.
[8] See also Pictet and Duparc, *ibid.*, 1887, **20**, 3415.

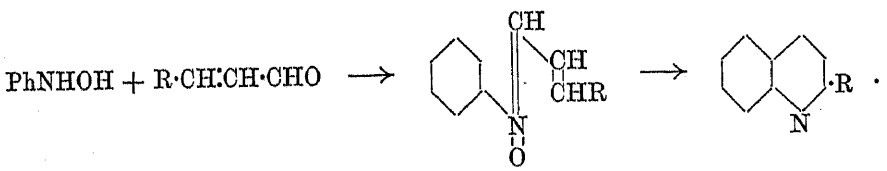
* There is also formed a certain amount of 6-ethylquinaldine, which may be due to migration of ethyl in ethylaniline with subsequent condensation, or to the attack of the *para* position by acetaldehyde, followed by reduction.

Busch and Koenigs [1] heated aniline hydrochloride and butylchloral hydrate with $ZnCl_2$ at 160–180°, the product being 3-chloroquinaldine:



Quinaldine has been isolated in small amount from a mixture of nitrobenzene and alcohol which had been exposed to light for some years.[2]

Bamberger and Weitnauer [3] condensed phenylhydroxylamine with α-unsaturated aldehydes, but the yields of quinoline derivatives were very small. There is first formed a "nitrone" (the oxide of a Schiff base):



(R = H, Me or Ph.)

Vogt and Nieuwland [4] formed acetaldehyde *in situ* from acetylene, 40% H_2SO_4 and $HgSO_4$; the yield of quinaldine was only 80 gms. from 400 gms. of aniline.

The following arylamines have been condensed with acetaldehyde (paraldehyde) by Döbner and v. Miller's method:

Amine.	*References.*
Aniline.	1, 4, 5, 6, 11, 17, 31, 44, 65, 67
o-Chloroaniline.	54
m-Chloroaniline.	54
p-Chloroaniline.	54, 58
m-Bromoaniline.	69
o-Bromoaniline.	54, 69
p-Nitroaniline.	68
Sulphanilic acid.	10
Arsanilic acid.	73
p-Aminodimethylaniline.	66
o-Aminoacetophenone.	26
p-Aminoacetophenone.	45
o-Aminobenzophenone.	19
p-Aminobenzophenone.	32
o-Toluidine.	5, 8, 11, 17
m-Toluidine.	5, 8
p-Toluidine.	5, 8, 17, 55, 62, 63, 64
3-Nitro-*p*-toluidine.	54
2 : 6-Diaminotoluene-4-sulphonic acid.	12, 14
4-*o*-Xylidine.	
4-*m*-Xylidine.	8, 11, 17, 28, 51, 60, 61, 62, 63
p-Amino-ethylbenzene.	67

[1] *Ber.*, 1891, **24**, 3962.
[2] Ciamician and Silber, *ibid.*, 1906, **39**, 4343.
[3] *Ibid.*, 1922, **55**, 3380.
[4] *J. A. C. S.*, 1921, **43**, 2076.

Amine.	*References.*
ψ-Cumidine.	15
o- and *p*-Aminophenols.	15
o-Anisidine.	15
p-Anisidine.	11
m-Phenetidine.	71 (fails)
p-Phenetidine.	71
Alkyl ethers of *p*-aminophenol (propyl, allyl, butyl, *iso*butyl, *iso*amyl)	73
o-, *m*-, *p*-Aminobenzoic acids.	13
m-Aminocinnamic acid.	35
p-Aminocinnamic acid.	20
3 : 5-Diamino-4-methylbenzoic acid.	48
α-Naphthylamine.	11, 15
β-Naphthylamine.	15, 33
β-Aminoanthraquinone.	9
β-Aminoanthraquinonesulphonic acid.	9
β-Aminoalizarine.	38
6-Aminoquinoline.	70
6-Aminokairoline.	70
4-Aminoquinaldine.	49
2-*p*-Aminostyrylquinoline.	36
m-Phenylenediamine.	41
Benzidine.	32

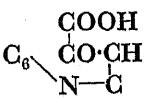
The Döbner–v. Miller synthesis has also been applied to the following arylamines and aldehydes. The α- and β-substituents in the resulting quinolines are indicated:

Amine.	*Aldehydes.*	*α.*	*β.*	*References.*
Aniline.	Acrolein.	H	H	2, 74
	Formald. and propionald.	H	Me	30, 42
	Acetald. and propionald. / Tiglic aldehyde.	Me	Me	29, 34
	Acetald. and *iso*butyrald.	·CHMe$_2$	H	29
	Acetald. and *m*-nitrobenzald.	NO$_2$·C$_6$H$_4$	H	18
	Butylchloral.	Me	Cl	43
	Propionald. (2 mols.).	Et	Me	16, 27, 30, 44, 52
	Propionald. and benzald.	Ph	Me	24
	Propionald. and *m*-nitrobenzald.	NO$_2$·C$_6$H$_4$	Me	24
	Butyrald. (2 mols.).	Pr	Et	16, 21
	*iso*Valerald. (2 mols.).	·CH$_2$CHMe$_2$	·CHMe$_2$	16, 22
	Œnanthald. (2 mols.).	C$_6$H$_{13}$	C$_5$H$_{11}$	16
	Cinnamaldehyde.	Ph	H	3, 7, 39, 53
m-Nitroaniline.	Œnanthald. (2 mols.).	C$_6$H$_{13}$	C$_5$H$_{11}$	40
p-Toluidine.	Acrolein.	—	—	74 (fails)
o-, *m*-, and *p*-Toluidines.	Propionald. (2 mols.).	Et	Me	23
p-Anisidine.	*m*-Nitrocinnamald.	NO$_2$·C$_6$H$_4$	H	30
Anthranilic acid.	Propionald. (2 mols.).	Et	Me	50
Anthranilic acid.	Œnanthaldehyde (2 mols.).	C$_6$H$_{13}$	C$_5$H$_{11}$	50
5-Aminoquinoline.	Œnanthaldehyde (2 mols.)	C$_6$H$_{13}$	C$_5$H$_{11}$	40
m-Phenylenediamine.	Œnanthaldehyde (4 mols.).	C$_6$H$_{13}$	C$_5$H$_{11}$	40

References.

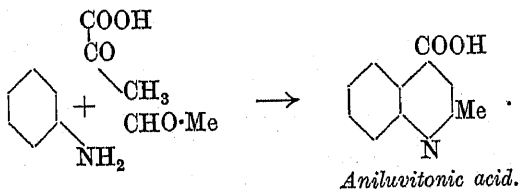
[1] Döbner and v. Miller, *Ber.*, 1881, **14**, 2812. [2] Leeds, *ibid.*, 1883, **16**, 289. [3] Döbner and v. Miller, *ibid.*, p. 1665. [4] Wallach and Wüsten, *ibid.*, p. 2007. [5] Döbner and v. Miller, *ibid.*, p. 2464. [6] Schultz, *ibid.*, p. 2600. [7] Grimaux, *Compt. rend.*, 1883, **96**, 984. [8] D.R.-P. 24317. [9] D.R.-P. 26197. [10] D.R.-P. 29819. [11] D.R.-P. 28217. [12] Berend, *Ber.*, 1884, **17**, 653. [13] Döbner and v. Miller,

ibid., p. 938. [14] Merz, *ibid.*, p. 1158. [15] Döbner and v. Miller, *ibid.*, p. 1698. [16] *Idem, ibid.*, p. 1712. [17] (Anon.) *Dingl. polyt. J.*, 1884, **250**, 533. [18] v. Miller and Kinkelin, *Ber.*, 1885, **18**, 1900. [19] Geigy and Koenigs, *ibid.*, p. 2405. [20] v. Miller and Kinkelin, *ibid.*, p. 3235. [21] Kahn, *ibid.*, p. 3361. [22] Spady, *ibid.*, p. 3373. [23] Harz, *ibid.*, p. 3384. [24] v. Miller and Kinkelin, *ibid.*, 1886, **19**, 525. [25] C. Beyer, *J. pr. Chem.*, 1886, **33**, 423. [26] O. Fischer, *Ber.*, 1886, **19**, 1036. [27] Kugler, *Dissn.*, Bonn, 1886. [28] Panajatow, *Ber.*, 1887, **20**, 32. [29] v. Miller, *ibid.*, pp. 1908, 1911. [30] v. Miller and Kinkelin, *ibid.*, pp. 1916, 1917, 1919. [31] Pictet and Duparc, *ibid.*, p. 3415. [32] Hinz, *Ann.*, 1887, **242**, 323, 326. [33] Seitz, *Ber.*, 1889, **22**, 254. [34] Rohde, *ibid.*, p. 267. [35] Eckhardt, *ibid.*, p. 271. [36] Bulach, *ibid.*, p. 285. [37] Rist, *ibid.*, 1890, **23**, 3483. [38] D.R.-P. 62703. [39] v. Miller, *Ber.*, 1891, **24**, 1720. [40] v. Miller and Gerdeissen, *ibid.*, p. 1731. [41] v. Miller and Niederländer, *ibid.*, p. 1740. [42] v. Miller, *ibid.*, p. 1900. [43] Busch and Koenigs, *ibid.*, p. 3962. [44] v. Miller, *ibid.*, 1892, **25**, 2072. [45] Berend and Thomas, *ibid.*, p. 2548. [46] Bischler, *ibid.*, p. 2864. [47] Marckwald and Berndt, *Ann.*, 1893, **274**, 354. [48] Marckwald and Busse, *ibid.*, p. 361. [49] Marckwald, *ibid.*, 1894, **279**, 22. [50] v. Niementowski and Orzechowski, *Ber.*, 1895, **28**, 2809. [51] v. Miller and Plöchl, *ibid.*, 1896, **29**, 1462. [52] Koenigs and Bischkopf, *ibid.*, 1901, **34**, 4327. [53] Murmann, *Zentr.*, 1904, ii, 454; *Monatsh.*, 1904, **25**, 621. [54] Bartow and McCollum, *J. A. C. S.*, 1904, **26**, 700. [55] Gasda, *Ber.*, 1905; **38**, 3699. [56] Decker and Remfry, *ibid.*, p. 2773. [57] Ciamician and Silber, *ibid.*, 1906, **39**, 4343. [58] D.R.-P. 204255. [59] Blaise and Maire, *Bull. Soc. chim.*, 1908, iv, **3**, 658. [60] Jones and White, *J. C. S.*, 1910, **97**, 639. [61] Jones and Evans, *ibid.*, 1911, **99**, 334. [62] Edwards, Garrod and Jones, *ibid.*, 1912, **101**, 1376. [63] Garrod, Jones and Evans, *ibid.*, p. 1389. [64] Fränkel and Löwy, *Ber.*, 1913, **46**, 2546. [65] Mikeska, Stewart and Wise. *J. Ind. Eng. Chem.*, 1919, **11**, 456. [66] Barbier, *Bull. Soc. chim.*, 1920, [iv], **27**, 427. [67] Mills, Harris and Lambourne, *J. C. S.*, 1921, **119**, 1294. [68] Hamer, *ibid.*, p. 1433. [69] Moudgill, *J. A. C. S.*, 1921, **43**, 2257. [70] Lindner, *Akad. Wiss. Wien*, 1921, **130**, 421; *Monatsh.*, 1922, **42**, 421. [71] Braunholtz, *J. C. S.*, 1922, **121**, 169; *J. A. C. S.*, 1922, **44**, 2967. [72] Bamberger and Weitnauer, *Ber.*, 1922, **55**, 3378. [73] Gutekunst and Gray, *J. A. C. S.*, 1922, **44**, 1741. [74] Mann, *J. C. S.*, 1922, **121**, 2178.

3. Döbner's pyruvic acid method: C_6 

By condensing aniline with pyruvic acid Böttinger [1] obtained a product, $C_{20}H_{18}O_4N_2$, which he called "aniluvitonic acid" by analogy with "uvitonic acid" from ammonia and pyruvic acid (see Pyridines, p. 220). This compound gave quinaldine and CO_2 when heated.[2]

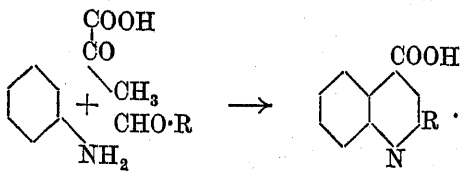
Döbner [3] showed that aniluvitonic acid resulted in better yield when aniline was condensed with an equimolecular mixture of pyruvic acid and acetaldehyde, and that Böttinger's synthesis was due to the partial conversion of the pyruvic acid into acetaldehyde by loss of CO_2 [4]:



Aniluvitonic acid.

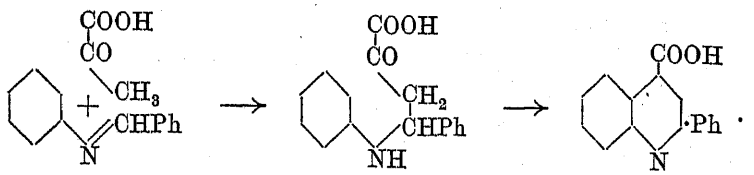
[1] *Ann.*, 1876, **188**, 336; 1877, **191**, 321; *Ber.*, 1881, **14**, 90; 1883, **16**, 2357.
[2] *Loc. cit.*; also Küsel, *Ber.*, 1887, **20**, 2249.
[3] *Ibid.*, p. 277.
[4] See also v. Miller and Lettenmayer, *ibid.*, 1891, **24**, 1918.

The method was extended by Döbner [1] to a variety of aldehydes:

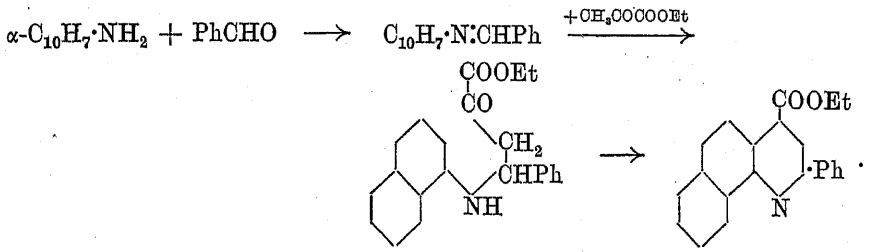


(R = methyl, ethyl, *iso*propyl, *iso*butyl, phenyl, furyl.)

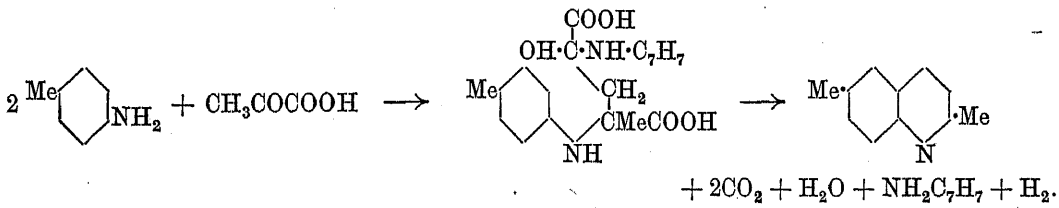
The mechanism of the reaction has been studied by Garzarolli-Thurnlackh,[2] Simon and Maugin,[3] and especially by Borsche.[4] The first named found that under Döbner's conditions (boiling alcoholic solution) pyruvic acid forms an additive compound with benzalaniline which may readily be converted into 2-phenylquinoline-4-carboxylic acid:



In the naphthalene series, Simon and Maugin obtained good results in cold chloroform or benzene, especially if pyruvic ester was substituted for the acid. For example:



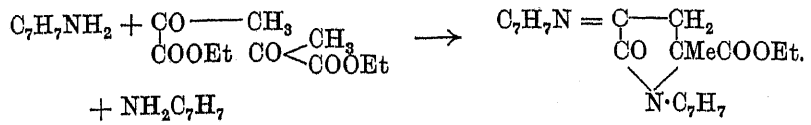
Simon studied the reaction between *p*-toluidine and pyruvic acid or ester alone. The *acid* gives first a derivative of glutaric acid, which is converted by boiling water into 6-methylquinaldine:



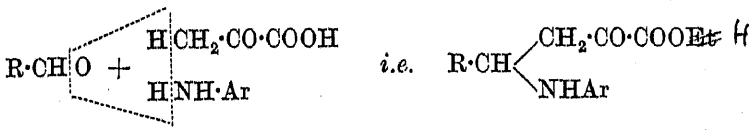
(As in other syntheses in this group, no free hydrogen is liberated; it is used up in the reduction of some product or intermediate.) [5]

[1] *Loc. cit.*; *Ann.*, 1887, **242**, 270–298.
[2] *Ber.*, 1899, **32**, 2274.
[3] *Compt. rend.*, 1907, **144**, 1275; Simon, *ibid.*, 1908, **146**, 1400; **147**, 125.
[4] *Ber.*, 1908, **41**, 3884; 1909, **42**, 4072.
[5] See Ciusa and Zerbini, *Gazz.*, 1920, **50**, ii, 317; Ciusa, *ibid.*, 1922, **52**, ii, 43.

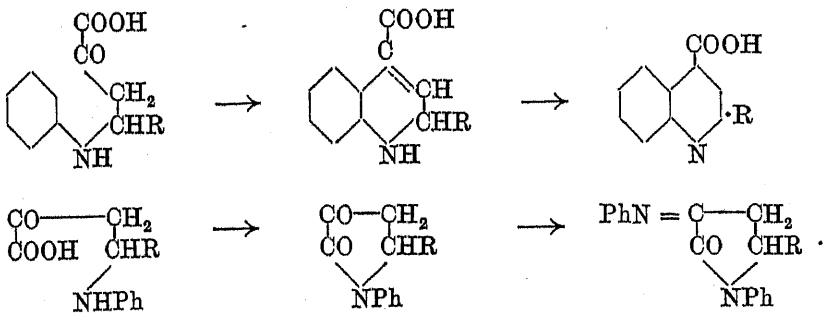
Pyruvic ester, on the other hand, gives as main product a pyrrole derivative:



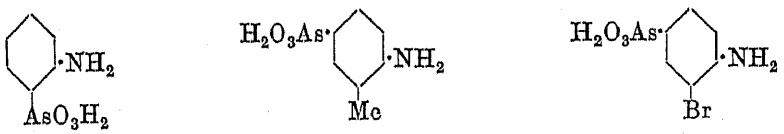
Borsche* showed that the primary product of the interaction of an arylamine, pyruvic acid and an aldehyde, namely:



may undergo ring-closure in two ways, giving in one case a dihydroquinoline and in the other a diketopyrrolidine. The former is converted as usual into the corresponding quinoline; the latter takes up a further molecule of base to form an anilide:



The proportions of the two products vary according to the amine, aldehyde and solvent used. In ether, the pyrrolidine is the main product; warm alcohol or acetic acid favours the formation of the quinoline. The three nitroanilines give no quinolines with benzaldehyde and pyruvic acid, indeed *o*-nitroaniline fails to react at all. Other ortho-substituted amines



have similarly been found to give neither the diketopyrrolidine nor the quinoline derivative.[1] The substituted pyruvic acids used by Borsche, namely:

Phenylpyruvic acid,	$PhCH_2 \cdot CO \cdot COOH$,
o-Nitrophenylpyruvic acid,	$NO_2 \cdot C_6H_4 \cdot CH_2 \cdot CO \cdot COOH$,
Benzoylpyruvic acid,	$PhCO \cdot CH_2 \cdot CO \cdot COOH$,
Benzylpyruvic acid,	$PhCH_2 \cdot CH_2 \cdot CO \cdot COOH$,

[1] Johnson and Adams, *J. A. C. S.*, 1923, **45**, 1307.

* See also pp. 43, 44.

gave as a rule only the pyrrolidine compound except in the case of β-naphthylamine. Benzylpyruvic acid, however, gave small amounts of quinolines when condensed with benzaldehyde and aniline or *m*-toluidine.

β-Naphthylamine shows a special facility for quinoline formation with any aldehyde (except α-hydroxyaldehydes) and any pyruvic acid.[1] The reaction with other arylamines frequently fails in the case of formaldehyde * or methylal,[2] and proceeds most easily with benzaldehyde.† That the Döbner synthesis is less general for aliphatic than for aromatic aldehydes is confirmed by the work of Johnson and Adams [3] upon quinolines from arsanilic acid.

Dehydrothiotoluidine gives no quinoline derivative by condensation with pyruvic acid and benzaldehyde.[4]

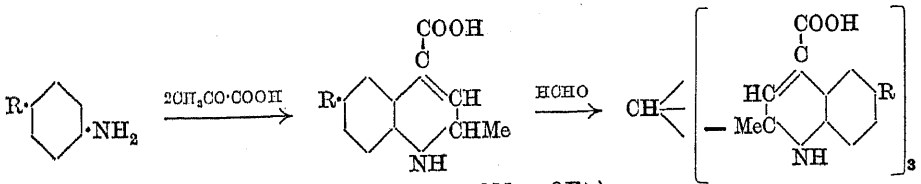
The following condensations by Döbner's method have been described:

I. *With pyruvic acid:*

Amine.	*Aldehyde.*	*References.*
Aniline.	Formaldehyde (fails).	12
	(Pyruvic acid).	13, 14
	Acetaldehyde.	1, 8
	Propionaldehyde.	2, 19
	*iso*Butyraldehyde.	2
	*iso*Valeraldehyde.	2
	Furfural.	43
	Benzaldehyde.	2, 3, 15, 37, 40
	p-Iodobenzaldehyde.	32
	o-Nitrobenzaldehyde.	26
	p-Dimethylaminobenzaldehyde.	38
	Salicylaldehyde.	4, 29.
	m- and *p*-Hydroxybenzaldehydes.	21
	Anisaldehyde.	38
	Piperonal.	24, 37
	Cuminaldehyde.	4
	2-Hydroxy-5-aldehydobenzoic acid.	34
	Cinnamaldehyde.	6
	α-Naphthaldehyde.	28
m- and *p*-Chloroanilines.	Benzaldehyde.	22
p-Iodoaniline.	Benzaldehyde.	32
o-, *m*- and *p*-Nitroanilines.	Benzaldehyde (fails).	22
m-Aminoacetanilide.	Benzaldehyde.	11

[1] See Döbner, *Ber.*, 1894, **27**, 352, 2020.
[2] Cf., for instance, Claus and Brandt, *Ann.*, 1894, **282**, 93; Pictet and Misner, *Ber.*, 1912, **45**, 1800.
[3] *J. A. C. S.*, 1923, **45**, 1307.
[4] Bogert and Meyer, *ibid.*, 1922, **44**, 1571.

* When formaldehyde is used in certain cases, the pyruvic acid alone may combine with the amine to give a dihydroquinoline, which then condenses with formaldehyde to yield a triquinolinylmethane (Döbner, *Ber.*, 1898, **31**, 686; 1900, **33**, 677):



(R = H, Me, ·OMe, ·OEt.)

† The "atophans" or α-phenylcinchoninic acids are used in pharmacy.

Amine.	*Aldehyde.*	*References.*
p-Aminoacetanilide.	Benzaldehyde.	31, 35
	p-Tolualdehyde.	35
	Anisaldehyde.	35
m-Aminodimethylaniline.	Benzaldehyde.	11
p-Aminoacetophenone.	Benzaldehyde.	22
o-Toluidine.	(Pyruvic acid).	13
	Benzaldehyde.	3
m-Toluidine.	Benzaldehyde.	22
p-Toluidine.	(Pyruvic acid).	13, 16, 21
	Benzaldehyde.	3, 37
	m-Aminobenzaldehyde.	31
	Piperonal.	27
	α-Naphthaldehyde.	28
4-*m*-Xylidine.	(Pyruvic acid).	13
o-Anisidine.	Benzaldehyde.	4
	Piperonal.	27, 37
p-Anisidine.	Formaldehyde.	30
	Acetaldehyde.	43
	(Pyruvic acid).	16, 43
	Benzaldehyde.	4, 12, 43
	p-Iodobenzaldehyde.	32
p-Phenetidine.	(Pyruvic acid).	14
6-Acetylamino-3-anisidine.	Benzaldehyde.	35
o-Aminophenol.	Benzaldehyde.	9
m-Aminophenol.	Benzaldehyde.	22
p-Aminophenol.	Formaldehyde (fails).	12
	Benzaldehyde.	9, 12
	Piperonal.	27
Anthranilic acid.	Benzaldehyde.	9
m- and *p*-Aminobenzoic acids.	Benzaldehyde (fails).	9
o-Aminosalicylic acid.	Benzaldehyde.	47
Arsanilic acid.	Benzaldehyde (fails).	42, 46
m-Phenylenediamine.	Benzaldehyde (2 mols.).	11
p-Phenylenediamine.	Benzaldehyde (2 mols.).	38
Benzidine.	Benzaldehyde (2 mols.).	25, 36
	Salicylaldehyde (2 mols.).	36
Tolidine.	Benzaldehyde (2 mols.).	25, 36
Dianisidine.	Benzaldehyde (2 mols.).	25, 36
α-Naphthylamine.	(Pyruvic acid).	13
	Benzaldehyde.	5
	Cinnamaldehyde.	7
ar.-Tetrahydro-*α*-naphthylamine.	Benzaldehyde.	45
β-Naphthylamine.	(Pyruvic acid).	13, 14
	Acetaldehyde.	10
	Propionaldehyde.	10
	*iso*Butyraldehyde.	10
	Œnanthaldehyde.	10
	Crotonaldehyde.	10
	Tiglic aldehyde.	10
	Citronellal.	10
	Citral.	10
	Aldol.	10
	Furfural.	10
	Benzaldehyde.	5, 20, 38, 39, 41
	Salicyaldehyde.	10, 38
	Anisaldehyde.	41
	Piperonal.	10, 41
	Vanillin.	10
	Cuminaldehyde.	10
	p-Dimethylaminobenzaldehyde.	38, 39
	Cinnamaldehyde.	7

Amine.	*Aldehyde.*	*References.*
1 : 4-Diaminonaphthalene.	Benzaldehyde (2 mols.).	23
5-Aminoquinoline.	Acetaldehyde.	18
	Benzaldehyde.	18
6-Aminoquinoline.	Acetaldehyde.	17
	Benzaldehyde.	17
Dehydrothiotoluidine.	Benzaldehyde (fails).	44

II. In addition, Borsche has described the following condensations (*Ber.*, 1909, **42**, 4072):

(a) *With phenylpyruvic acid,* $PhCH_2 \cdot CO \cdot COOH$:

Amine.	*Aldehyde.*	*Yield of Quinoline.*
Aniline.	Formaldehyde.	nil.
	Benzaldehyde.	nil.
	p-Nitrobenzaldehyde.	nil.
	Salicylaldehyde.	nil.
	Anisaldehyde.	nil.
o-, *m*-, and *p*-Toluidines.	Benzaldehyde.	nil.
m-Nitroaniline.	Benzaldehyde.	nil.
β-Naphthylamine.	Formaldehyde.	22–25%
	Acetaldehyde.	—
	Benzaldehyde.	40%

(b) *With o-nitrophenylpyruvic acid,* $NO_2 \cdot C_6H_4 \cdot CH_2 \cdot CO \cdot COOH$:

Aniline.	Benzaldehyde.	nil.
β-Naphthylamine.	Formaldehyde.	22%
	Benzaldehyde.	33%

(c) *With benzoylpyruvic acid,* $PhCO \cdot CH_2 \cdot CO \cdot COOH$:

Aniline.	Benzaldehyde.*	nil.
	Anisaldehyde.	nil.
β-Naphthylamine.	Formaldehyde.	34%
	Benzaldehyde.	25%

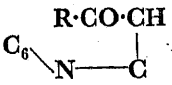
(d) *With benzylpyruvic acid,* $PhCH_2 \cdot CH_2 \cdot CO \cdot COOH$:

Aniline.	Benzaldehyde.	13%
m-Toluidine.	Benzaldehyde.	18%
β-Naphthylamine.	Benzaldehyde.	57%

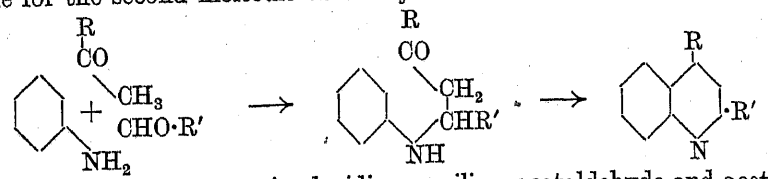
References.

[1] Döbner, *Ber.*, 1887, **20**, 277. [2] *Idem*, *Ann.*, 1887, **242**, 265. [3] Döbner and Gieseke, *ibid.*, p. 290. [4] Döbner, *ibid.*, 1888, **249**, 98. [5] Döbner and Kuntze, *ibid.*, p. 109. [6] Döbner and Peters, *Ber.*, 1889, **22**, 3307. [7] *Idem*, *ibid.*, 1890, **23**, 1228. [8] v. Miller, *ibid.*, 1891, 24, 1900. [9] Döbner and Fettback, *Ann.*, 1894, **281**, 1. [10] Döbner, *Ber.*, 1894, **27**, 352, 2020. [11] Döbner and Ferber, *Ann.*, 1894, **281**, 15. [12] Claus and Brandt, *ibid.*, **282**, 85. [13] Simon, *Ann. chim.*, 1896, vii, **19**, 433–536. [14] Döbner, *Ber.*, 1898, **31**, 686. [15] Garzarolli-Thurnlackh, *ibid.*, 1899, **32**, 2274. [16] Döbner and Bischkopf, *ibid.*, 1900, **33**, 677. [17] Willgerodt and Jablowski, *ibid.*, p. 2918. [18] Willgerodt and v. Neander, *ibid.*, p. 2928. [19] Koenigs and Bischkopf, *ibid.*, 1901, **34**, 4327. [20] Simon and Maugin, *Compt rend.*, 1907, **144**, 1275. [21] Simon, *ibid.*, 1908, **146**, 1400; **147**, 125. [22] Borsche, *Ber.*, 1908, **41**, 3884. [23] Finger and Spitz, *J. pr. Chem.*, 1909, **79**, 445. [24] D.R.-P. 244497. [25] D.R.-P. 246078. [26] D.R.-P. 279195. [27] D.R.-P. 281603. [28] D.R.-P. 284232. [29] D.R.-P. 284233. [30] Pictet and Misner, *Ber.*, 1912, **45**, 1800. [31] D.R.-P. 287216. [32] D.R.-P. 288303. [33] D.R.-P. 292393. [34] D.R.-P. 293467. [35] D.R.-P. 294159. [36] Fr. P. 440669. [37] Fr. P. 445529 with addition 19231/1914. [38] Ciusa and Lazzatto, *Gazz.*, 1914, **44**, i, 64. [39] Ciusa, *R. A. L.*, 1914, **23**, ii, 262; *Gazz.*, 1916, **46**, i, 135; Ciusa and Borgo, *R. A. L.*, 1914, **23**, ii, 265. [40] Boehm and Bournot, *Ber.*, 1915, **48**, 1570. [41] Ciusa and Zerbini, *Gazz.*, 1920, **50**, ii, 317. [42] Johnson and Adams, *J. A. C. S.*, 1921, **43**, 2255. [43] Halberkann, *Ber.*, 1921, **54**, 3090. [44] Bogert and Meyer, *J. A. C. S.*, 1922, **44**, 1571; Meyer, *Chem. News*, 1922, **124**, 319. [45] v. Braun and Wolff, *Ber.*, 1922, **55**, 3675. [46] Johnson and Adams, *J. A. C. S.*, 1923, **45**, 1313. [47] D. Pat. Anm. R. 43677.

* See Schiff and Gigli, *Ber.*, 1898, **31**, 1308, who also condensed acetylpyruvic ester with benzalaniline, but obtained only the diketopyrrolidine.

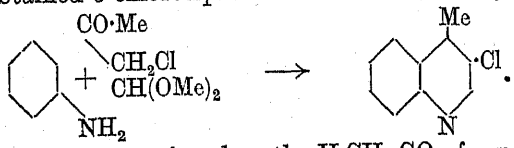
4. Beyer's method: 

Beyer's modification * of the Döbner–Miller synthesis consists in the substitution of a methyl ketone for the second molecule of aldehyde : [1]



Thus aniline, methylal and acetone give lepidine; aniline, acetaldehyde and acetophenone yield 2-methyl-4-phenylquinoline. It will be observed that the γ-substituent is supplied by the ketone, the α-substituent by the aldehyde.

Pictet and Misner [2] obtained 3-chlorolepidine from aniline, methylal and chloroacetone :



The $Cl{\cdot}CH_2{\cdot}CO{\cdot}$ is evidently more reactive than the $H{\cdot}CH_2{\cdot}CO{\cdot}$, for no trace of ω-chlorolepidine is obtained.

Quinolines have been prepared by Beyer's method in the following cases :

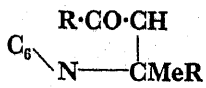
Amine.	*Aldehyde.*	*Ketone.*	*References.*
Aniline.	Formaldehyde.	Acetone.	2, 12
	Acetaldehyde.	Acetone.	2
	Acetaldehyde.	Acetophenone.	2
	Formaldehyde.	Chloroacetone.	8
p-Toluidine.	Formaldehyde.	Acetone.	12
	Acetaldehyde.	Acetone.	5
	Acetaldehyde.	Acetophenone.	9
4-*m*-Xylidine.	Acetaldehyde.	Acetone.	13
5-*m*-Xylidine.	Acetaldehyde.	Acetone.	13
p-Xylidine.	Acetaldehyde.	Acetone.	13
p-Anisidine.	Formaldehyde.	Acetone.	8
	Acetaldehyde.	Acetone.	7
	Acetaldehyde.	Acetophenone.	6
p-Phenetidine.	Formaldehyde.	Acetone.	12
	Acetaldehyde.	Acetone.	11, 14
p-Aminodimethylaniline.	Formaldehyde.	Acetone.	10
α-Naphthylamine.	Acetaldehyde.	Acetone.	3
β-Naphthylamine.	Formaldehyde.	Acetone.	3
	Acetaldehyde.	Acetone.	1, 3
Benzidine.	Acetaldehyde.	Acetone.	4

References.

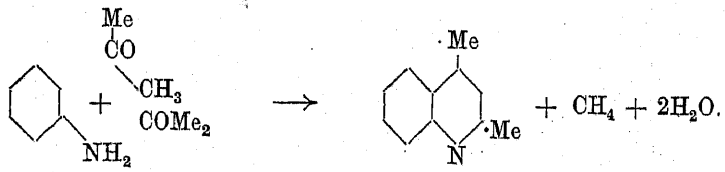
[1] Reed, *J. pr. Chem.*, 1885, **32**, 630. [2] Beyer, *ibid.*, 1886, **33**, 393; *Ber.*, 1887, **20**, 1767. [3] Reed, *J. pr. Chem.*, 1887, **35**, 298. [4] Schestapol, *Ber.*, 1887, **20**, 2506. [5] Pfitzinger, *J. pr. Chem.*, 1888, **38**, 40. [6] Koenigs and Jaeglé, *Ber.*, 1895, **28**, 1046. [7] Koenigs and Mengel, *ibid.*, 1904, **37**, 1322. [8] Pictet and Misner, *ibid.*, 1912, **45**, 1800. [9] Fischer, Scheibe, Merkel and Müller, *J. pr. Chem.*, 1919, **100**, 91. [10] Barbier, *Bull. Soc. chim.*, 1920, [iv], **27**, 434. [11] Mikeska, Haller and Adams, *J. A. C. S.*, 1920, **42**, 2392. [12] Mikeska, *ibid.*, p. 2396. [13] Mikeska and Adams, *ibid.*, p. 2394. [14] Palkin and Harris, *J. Ind. Eng. Chem.*, 1922, **14**, 704.

[1] Beyer, *J. pr. Chem.*, 1886, **33**, 393; *Ber.*, 1887, **20**, 1767. [2] *Ibid.*, 1912, **45**, 1800.

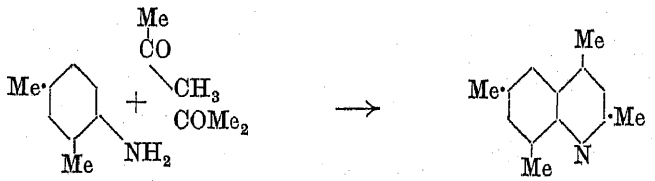
* This method is usually known as Beyer's, though the first example—β-naphthylamine, acetaldehyde, and acetone—was described by Reed in 1885.

5. Riehm's method from arylamines and ketones: 

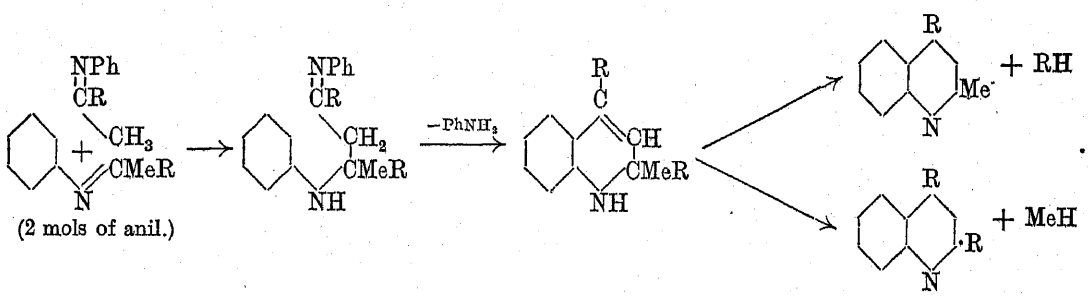
A remarkable group of reactions involving ring-closure and elimination of a methyl group as CH_4 was discovered by Riehm in 1885. Engler and Riehm [1] heated together aniline hydrochloride and acetone for three days, with or without $AlCl_3$, PCl_5, etc., and obtained 2 : 4-dimethylquinoline and a gas which proved to be methane:



Acetanilide or benzanilide with acetone and zinc chloride at 200° gave the same dimethylquinoline in 8% yield.[2] Levin and Riehm [3] obtained 2 : 4 : 6 : 8-tetramethylquinoline in 30% yield from 4-*m*-xylidine and acetone:



The recent experiments of Knoevenagel [4] upon ketone anils have suggested an explanation of these reactions. Knoevenagel has shown that excellent yields of 2 : 4-substituted quinolines are obtained when the anils of acetone, acetophenone or methyl ethyl ketone are heated with HCl at 180–200°:



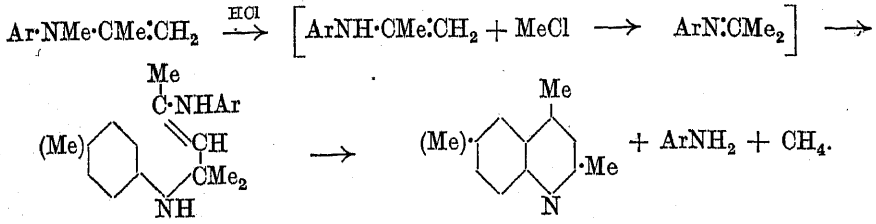
(R = Me, Et or Ph.)

The *p*-tolils of acetone and methyl ethyl ketone behave similarly. Acetone anil is also converted into 2 : 4-dimethylquinoline by heat alone at 280° (81% yield), by heating with phosphorus and HI (91% yield) and less smoothly by heating with $AlCl_3$.

The acetone derivatives of methylaniline and methyl-*p*-toluidine, which have the structure

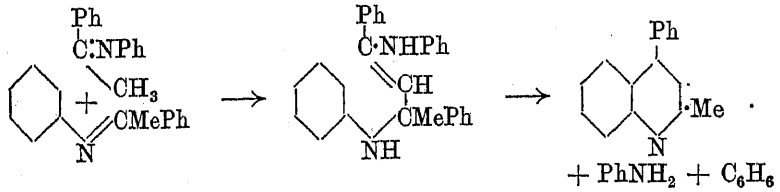
[1] *Ber.*, 1885, **18**, 2245. [2] Riehm, *Ann.*, 1887, **238**, 9. [3] *Ber.*, 1886, **19**, 1394.
[4] Knoevenagel and Bähr, *ibid.*, 1922, **55**, 1923; Knoevenagel and Goos, *ibid.*, p. 1934; Knoevenagel, *ibid.*, 1923, **56**, 2414.

$Ar{\cdot}NMe{\cdot}CMe{:}CH_2$, are demethylated by HCl at 180–200° and the resulting acetone anil and acetone *p*-tolil give quinolines in the usual manner:



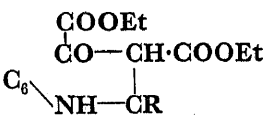
Mesityl oxide and aniline hydrochloride yield 2 : 4-dimethylquinoline at 180°, methane being evolved (but no methyl chloride). Phorone refluxed with aniline and a trace of iodine gives acetone-anil but no quinoline derivative.

In the case of acetophenone-anil benzene is eliminated in the last stage in preference to methane *:



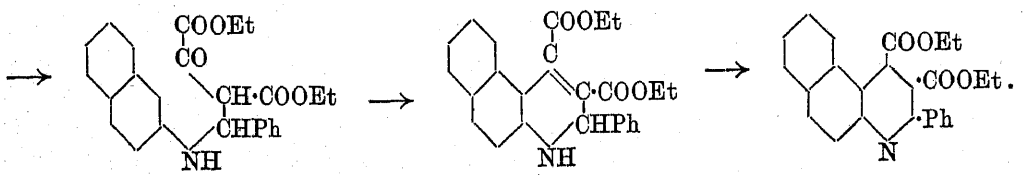
The process is covered by D.R.-PP. 363582/3 of 1921, in which is described the preparation of quinaldines from aniline and *p*-toluidine with acetone and from aniline with methyl ethyl ketone and acetophenone. In each case the heavier group of the ketone supplies the *γ*-substituent, but is eliminated as hydrocarbon from the *α*-position, leaving a quinaldine.

6. From oxalacetic silver, aldehydes and arylamines:



Oxalacetic ester, $COOEt{\cdot}CH_2{\cdot}CO{\cdot}COOEt$, is a carboxylated pyruvic ester and may be used in place of pyruvic acid in the Döbner synthesis. Simon and Conduché [1] showed that benzal-*β*-naphthylamine forms an additive compound with oxalacetic ester, which is converted by conc. H_2SO_4 into a dihydro-*β*-naphthoquinoline. This readily loses two hydrogen atoms and gives 2-phenyl-*β*-naphthoquinoline-3 : 4-dicarboxylic ester:

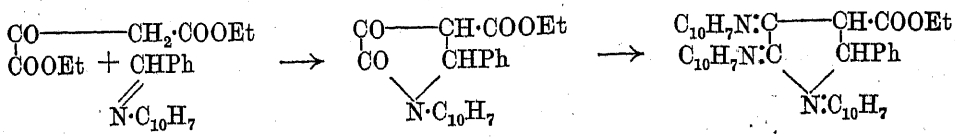
$\beta\text{-}C_{10}H_7{\cdot}N{:}CHPh + COOEt{\cdot}CH_2{\cdot}CO{\cdot}COOEt.$



[1] *Compt. rend.*, 1904, **139**, 297.

* A little *symm.*-triphenylbenzene is also produced.

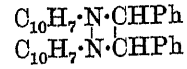
As with pyruvic acid, there is here also a tendency to form diketopyrrolidines [1]:



and this limits the application of the method.

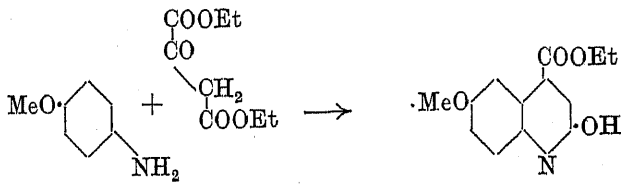
α-Naphthylamine and amines of the benzene series give no quinolines, but the reaction succeeds with β-naphthylamine and benzaldehyde, anisaldehyde or *m*-nitrobenzaldehyde. Piperonal gives only the pyrrolidine, while salicylaldehyde and vanillin yield no cyclic compounds.[2]

Ciusa [3] from benzal-β-naphthylamine and oxalacetic ester obtained, in addition to Simon's additive product, two by-products, 2-phenyl-β-naphthoquinolinedicarboxylic ester and a compound, $C_{34}H_{26}N_2$, to which he gave the constitution:

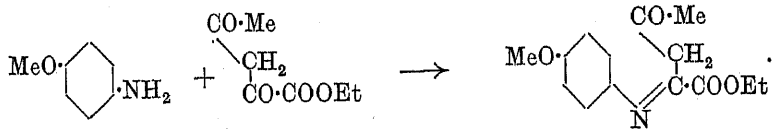


i.e. bimolecular benzal-β-naphthylamine.

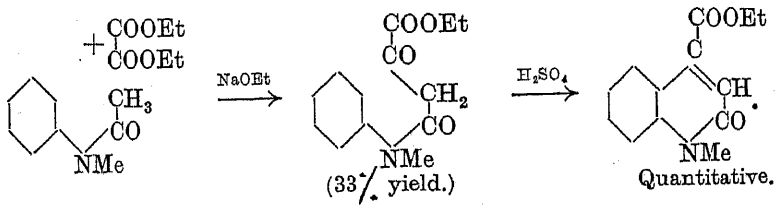
Halberkann [4] prepared a quinoline from anisidine and oxalacetic ester alone by a quite different reaction:



Two methods described by Thielepape [5] may be mentioned here. In the first, *p*-anisidine was condensed with acetone-oxalic ester, but no quinoline derivative could be obtained:



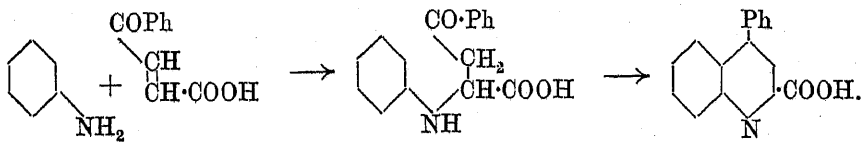
The second was more successful. *N*-Methylacetanilide was converted into the oxalacetic derivative by means of oxalic ester and NaOEt. The product gave *N*-methylcarbostyril-4-carboxylic ester when treated with conc. H_2SO_4:



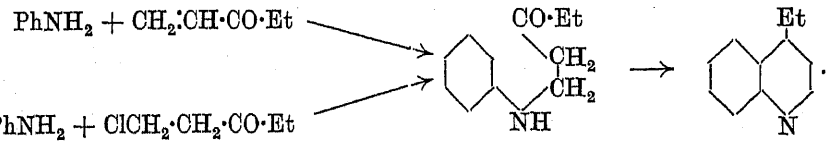
[1] Schiff and Bertini, *Ber.*, 1897, **30**, 601.
[2] Simon and Conduché, *loc. cit.*; Simon and Maugin, *Compt. rend.*, 1906, **143**, 427, 466; *Ann. chim.*, 1908, [viii], **13**, 361. [3] *Gazz.*, 1922, **52**, ii, 44. [4] *Ber.*, 1921, **54**, 3090. [5] *Ibid.*, 1922, **55**, 127.

7. From unsaturated ketones and arylamines: $C_6\langle^{NH-C(CH)(CO\cdot R)}$

Koenigs and Meimberg [1] obtained 4-phenylquinoline-2-carboxylic acid in 15–20% yield by condensing together aniline and benzoylacrylic acid:



This reaction has been extended by Blaise and Maire.[2] Aniline and vinyl ethyl ketone at 45° form an additive compound, which may be more conveniently prepared by treating β-chlorodiethyl ketone with two molecular proportions of aniline at 100°. This product is unchanged by the usual dehydrating agents, but gives 4-ethylquinoline when heated with aniline hydrochloride or diethylaniline hydrochloride:

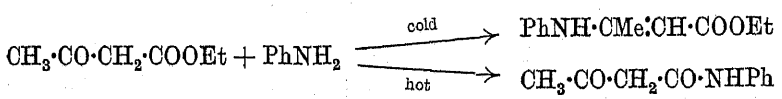


A mixture of aniline, aniline hydrochloride and β-chlorodiethyl ketone in alcohol, saturated with HCl, gives ethylquinoline directly, though in smaller yield (20%). Similar results are obtained with methylaniline or anthranilic acid, and with aniline and vinyl propyl ketone.

The method is a development of Beyer's synthesis (sect. 4).

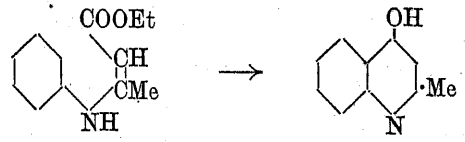
8. From β-diketones or β-keto-esters: $C_6\langle^{NH-C(CH)(CO\cdot R)}$

Acetoacetic ester reacts with aniline in two ways. In the cold the product is phenyl-β-aminocrotonic ester (the conditions for a quantitative yield have been worked out by Stark [3]). At the boiling point, acetoacetic anilide is formed [4]:



[1] *Ber.*, 1895, **28**, 1049.
[2] *Compt. rend.*, 1907, **144**, 93; *Bull. Soc. chim.*, 1908, [iv], **3**, 658, 667.
[3] *Ber.*, 1907, **40**, 3431.
[4] Knorr, *ibid.*, 1892, **25**, 772.

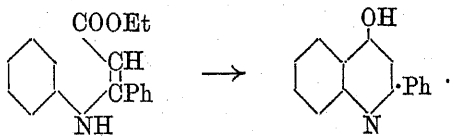
Both products condense to quinolines when treated with conc. H_2SO_4:

(i) 

(ii) 

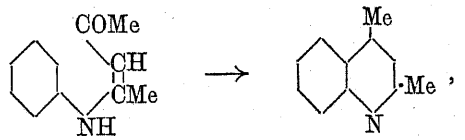
(*a*) Reaction (i) was used by Conrad and Limpach [1] for the synthesis of 4-hydroxyquinaldines from a variety of arylamines. Condensation may be brought about by conc. H_2SO_4 or by boiling dilute HCl or by heating for a very short time at 240°.

Benzoylacetic ester behaves rather differently from acetoacetic ester, the unsaturated phenylamino ester being readily formed even at higher temperatures. Conc. H_2SO_4 converts the product into the corresponding 4-hydroxyquinoline [2]:

$PhNH_2 + PhCO{\cdot}CH_2{\cdot}COOEt \longrightarrow$ 

Wislicenus [3] has similarly obtained quinolines from formylphenylacetic ester, H·CO·CHPh·COOMe, with aniline and with *p*-xylidine.

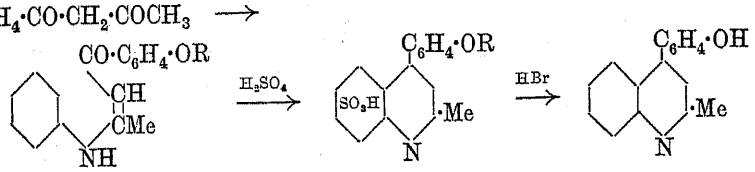
β-Diketones, such as acetylacetone, also react with arylamines to give unsaturated amines readily convertible into quinolines by means of conc. H_2SO_4. This reaction was first used by Combes [4]:

$PhNH_2 + CH_3COCH_2COCH_3 \longrightarrow$ 

and is the best method of preparing 2 : 4-dimethylquinolines.[5]

Quinaldines substituted in the 4-position by a hydroxyphenyl or alkyloxyphenyl group have found application in medicine. They are most readily prepared by Combes' method: [6]

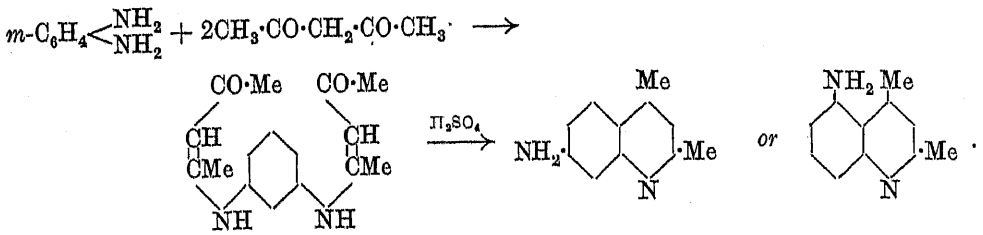
$PhNH_2 + m$- or p-$RO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}COCH_3 \longrightarrow$



(R = Me or Et.)

[1] *Ber.*, 1887, **20**, 944, 948. [2] Knorr, *Ann.*, 1888, **245**, 378. [3] See also Börner, *Dissn. Wurzburg*, 1899.
[4] *Compt. rend.*, 1887, **106**, 142; *Bull. Soc. chim.*, 1888, [iv], **49**, 90.
[5] Fischer, Scheibe, Merkel and Müller, *J. pr. Chem.*, 1919, **100**, 91; v. Braun, Gmelin and Schultheiss, *Ber.*, 1923, **56**, 1346. [6] Besthorn and Jaeglé, *ibid.*, 1894, **27**, 907, 3035; D.R.-P. 79173.

m-Phenylenediamine reacts with two molecular proportions of acetylacetone, but on ring-closure half the diketone is regenerated and the product is 5- (or 7-) aminodimethylquinoline :[1]

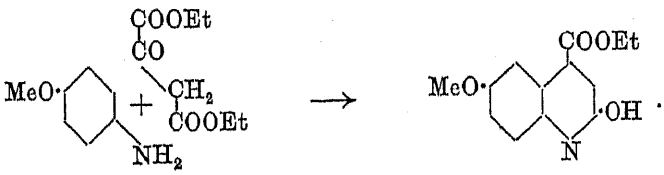


p-Phenylenediamine fails to give a quinoline derivative.[2]

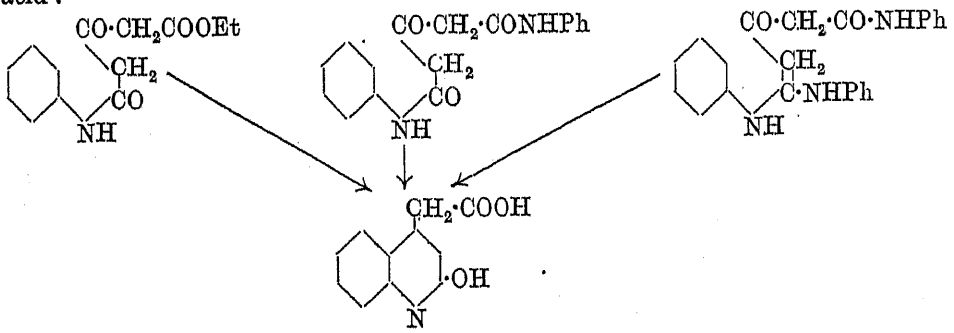
Bülow and Issler[3] condensed *m*-aminophenol with several diketones, obtaining the corresponding hydroxyanilides in 60–80% yield. These were converted into quinolines (25–48% yield) by passing HCl gas into the solution in acetic acid.

(*b*) As has been mentioned above, the normal anilide of acetoacetic acid yields 4-methylcarbostyril when treated with conc. H_2SO_4. Knorr[4] applied this method to a number of arylamines. A considerable improvement was effected by Ewins and King;[5] the amine is boiled with the keto-ester for a few minutes only (instead of several hours at 150–160°) and the anilide so obtained is warmed at 100° for 10–15 minutes with conc. H_2SO_4 (instead of being poured into the cold acid). Under these conditions the yield is 55% in the first stage and quantitative in the second.

Oxalacetic ester (but *not* a mixture of pyruvic and orthoformic esters) condenses with *p*-anisidine to give 6-methoxycarbostyril-4-carboxylic ester :[6]

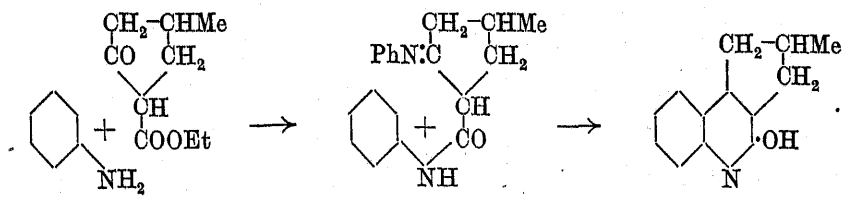


From acetonedicarboxylic ester and aniline at 100° Besthorn and Garben[7] obtained a mixture of anilide, dianilide and trianilide, each of which is converted by conc. H_2SO_4 into carbostyril-4-acetic acid :



[1] Marckwald and Schmidt, *Ann.*, 1893, **274**, 367–376. [2] *Idem, ibid.* [3] *Ber.*, 1903, **36**, 2447, 4013.
[4] *Ibid.*, 1884, **17**, 2870; *Ann.*, 1886, **236**, 69–115; 1888, **245**, 357–388; D.R.-P. 26428.
[5] *J. C. S.*, 1913, **103**, 104. [6] Halberkann, *Ber.*, 1921, **54**, 3090. [7] *Ibid.*, 1900, **33**, 3439, 3448.

3-Methyl*cyclo*pentanone-5-carboxylic ester is a cyclic substituted acetoacetic ester and has been converted into the corresponding carbostyril by Dieckmann :[1]



The following condensations have been described :

i. *γ-Hydroxyquinolines from β-keto-esters (Conrad and Limpach's method)* :

Keto-ester.	*Amine.*	*References.*
Acetacetic ester.	Aniline.	2, 3, 4, 10
	o- and *p*-Toluidines.	5
	4-*m*-Xylidine.	5, 13
	ψ-Cumidine.	5
	o- and *p*-Anisidines.	5
	m-Aminophenol.	8
	α- and β-Naphthylamines.	5
	1 : 4-Diaminonaphthalene (double).	11
Methylacetoacetic ester. Ethylacetoacetic ester.	Aniline.	7
Formylacetic ester. ✓	Aniline. ✓	9, 12
	p-Xylidine.	12
	4-*m*-Xylidine (fails).	13
Benzoylacetic ester.	Aniline.	6
β-Phenylamino-α-bromocrotonic acid.		1

References.

[1] Knorr and Antrick, *Ber.*, 1884, **17**, 2870. [2] Conrad and Limpach, *ibid.*, 1887, **20**, 944, 948. [3] Knorr, *ibid.*, p. 1397. [4] D.R.-P. 42276. [5] Conrad and Limpach, *Ber.*, 1888, **21**, 523, 1649, 1965. [6] Knorr, *Ann.*, 1888, **245**, 378. [7] Conrad and Limpach, *Ber.*, 1891, **24**, 2990. [8] v. Pechmann and Schwarz, *ibid.*, 1899, **32**, 3686, 3699. [9] Börner, *Dissn. Wurzburg*, 1899. [10] Stark, *Ber.*, 1907, **40**, 3431. [11] Finger and Spitz, *J. pr. Chem.*, 1909, **79**, 445. [12] Wislicenus, *Ann.*, 1917, **413**, 248. [13] Späth, *Monatsh.*, 1919, **40**, 93.

ii. 2 : 4-*Substituted quinolines from β-diketones (Combes' method)* :

Diketone.	*Amine.*	*References.*
Acetylacetone.	Aniline.	1, 8, 10, 13, 14
	o-Toluidine.	1
	p-Toluidine.	1, 9, 11
	p-Anisidine (fails).	8
	m-Aminophenol.	7
	m-Phenylenediamine.	3
	p-Phenylenediamine (fails).	3
Methylacetylacetone.	Aniline.	1
Formylacetone.	Aniline (fails).	12
Benzoylacetone.	Aniline.	2, 5, 10
	p-Toluidine.	10
	*m*Aminophenol.	7
	p-Anisidine (fails).	5
m- and *p*-Methoxy- and *o*- and *p*-Ethoxy-benzoylacetones.	Aniline.	4, 6
Propionylacetophenone. Butyrylacetophenone. Benzoylacetophenone.	*m*-Aminophenol.	7
Oxalacetic ester.	*p*-Anisidine (fails).	12
Acetoneoxalic ester.	*p*-Anisidine (fails).	12

[1] *Ann.*, 1901, **317**, 91.

References.

[1] Combes, *Compt. rend.*, 1887, **106**, 142; *Bull. Soc. chim.*, 1888, [iii], **49**, 90. [2] Beyer, *Ber.*, 1887, **20**, 1767. [3] Marckwald and Schmidt, *Ann.*, 1893, **274**, 367. [4] Besthorn and Jaeglé, *Ber.*, 1894, **27**, 907, 3035. [5] Koenigs and Meimberg, *ibid.*, 1895, **28**, 1038. [6] D.R.-P. 79173. [7] Bülow and Issler, *ibid.*, 1903, **36**, 2447, 4013. [8] Koenigs and Mengel, *ibid.*, 1904, **37**, 1325, 1333. [9] Ferriss and Turner, *J. C. S.*, 1920, **117**, 1145. [10] Fischer and Scheibe, *J. pr. Chem.*, 1920, **100**, 91–105. [11] Fischer, Müller and Merkel, *ibid.* [12] Thielepape, *Ber.*, 1922, **55**, 129. [13] Scheibe, *ibid.*, 1923, **56**, 148. [14] v. Braun, Gmelin and Schultheiss, *ibid.*, p. 1346.

iii. *α-Hydroxyquinolines (carbostyrils) from β-keto-esters (Knorr's method):*

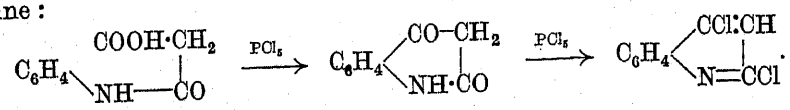
Keto-ester.	*Amine.*	*References.*
Acetoacetic ester.	Aniline.	1, 2, 3, 4, 7, 21
	Methylaniline.	5, 6, 7
	o-Toluidine.	2, 3, 8, 17
	m-Toluidine.	2, 8, 17
	p-Toluidine.	2, 3, 8, 17
	Xylidines.	2
	Cumidine.	2
	β-Naphthylamine.	2, 3
	Anthranilic acid.	2, 9
	4-Methylanthranilic acid.	9
	m-Phenylenediamine.	10
	2 : 4-Tolylenediamine.	10
	1 : 5-Diaminonaphthalene (single).	16
	Benzidine (single and double).	12
Methylacetoacetic ester.	Aniline.	8
Ethylacetoacetic ester.	Anthranilic acid.	9
	4-Methylanthranilic acid.	9
	m-Phenylenediamine.	11
Formylphenylacetic ester.	Aniline.	18
Oxalacetic ester.	Aniline.	20
	p-Anisidine.	19, 20
Acetonedicarboxylic ester.	Aniline.	13
	m-Phenylenediamine.	14
3-Methyl*cyclo*pentanone-5-carboxylic ester.	Aniline.	15

References.

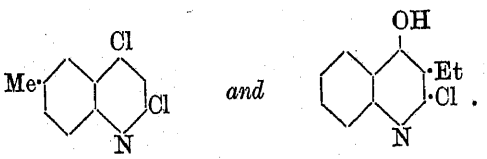
[1] Knorr, *Ber.*, 1883, **16**, 2593. [2] D.R.-P. 26428. [3] Knorr, *Ber.*, 1884, **17**, 540. [4] (Anon.) *Dingl. polyt. J.*, 1884, **250**, 533. [5] Knorr and Antrick, *Ber.*, 1884, **17**, 2870. [6] D.R.-P. 32281. [7] Knorr, *Ann.*, 1886, **236**, 83, 106. [8] *Idem, ibid.*, 1888, **245**, 358, 365, 368, 370. [9] v. Niementowski, *J. C. S.*, Abstr. 1894, i, 259; *Ber.*, 1894, **27**, 1394. [10] Besthorn and Byvanck, *Ber.*, 1898, **31**, 796. [11] Byvanck, *ibid.*, p. 2145. [12] Heidrich, *Monatsh.*, 1893, **19**, 690. [13] Besthorn and Garben, *Ber.*, 1900, **33**, 3439. [14] *Idem, ibid.*, p. 3448. [15] Dieckmann, *Ann.*, 1901, **317**, 91. [16] Finger and Spitz, *J. pr. Chem.*, 1909, **79**, 445. [17] Ewins and King, *J. C. S.*, 1913, **103**, 104. [18] Wislicenus and Erbe, *Ann.*, 1920, **421**, 146. [19] Halberkann, *Ber.*, 1921, **54**, 3090. [20] Thielpape, *ibid.*, 1922, **55**, 131. [21] Diepolder and Deuerlein, *J. pr. Chem.*, 1923, **106**, 58.

9. From anilides etc. of malonic acid: $C_6<\!\!\begin{smallmatrix}N\!-\!C(COOH)\\ \quad\quad\quad\quad |\\ \quad\quad\quad\quad C\end{smallmatrix}$

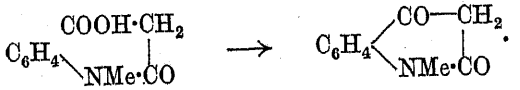
By the action of PCl_5 upon the semianilide of malonic acid Rügheimer [1] obtained 2 : 4-dichloroquinoline:



The method has been extended by Rügheimer and Hofmann [2] to the *p*-toluidide and by Rügheimer and Schramm [3] to the anilide of ethylmalonic acid, the products being respectively:

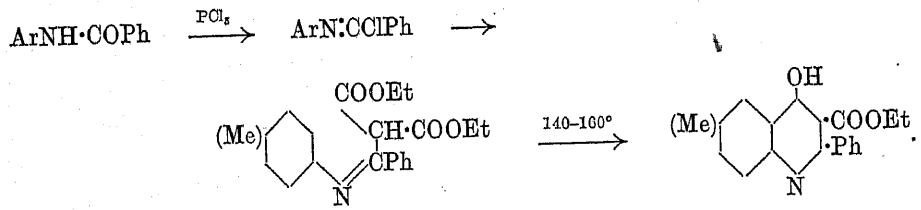


Kayser and Reissert [4] obtained only a small yield of *N*-methyl-4-hydroxycarbostyril from methylaniline:



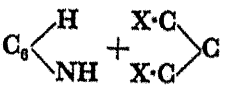
10. From aromatic imide-chlorides and malonic ester: $C_6<\!\!\begin{smallmatrix}N\!-\!C(COOEt)\\ \quad\quad\quad\quad |\\ \quad\quad\quad\quad C\end{smallmatrix}$

Just [5] obtained quinoline derivatives by heating to 140–160° the condensation products of sodiomalonic ester with aromatic imide-chlorides:

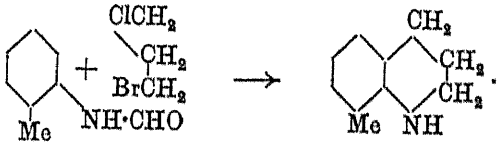


(Ar = phenyl or *p*-tolyl.)

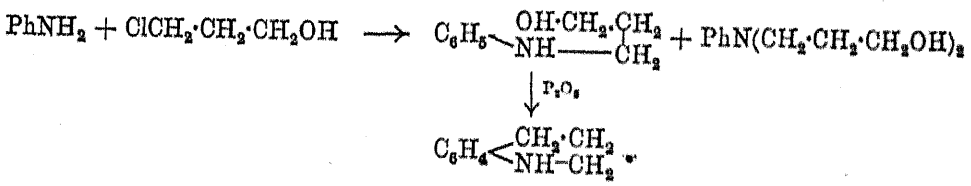
[1] *Ber.*, 1884, **17**, 736; 1885, **18**, 2475.
[2] *Ibid.*, p. 739; 1885, **18**, 2979.
[3] *Ibid.*, 1887, **20**, 1235.
[4] *Ibid.*, 1882, **25**, 1201.
[5] *Ibid.*, 1885, **18**, 2632; **19**, 1462, 1541; D.R.-P. 33497.

11. From arylamines and trimethylene dihalides: 

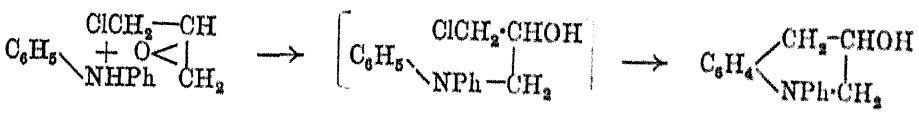
The julolidine synthesis (p. 389) leads to a tetrahydroquinoline when applied to *o*-toluidine:[1]



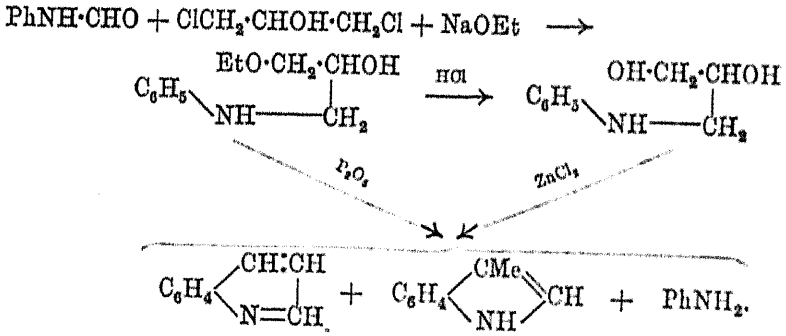
Rindfusz and Harnack[2] condensed aniline with trimethylene chlorohydrin and isolated both the secondary and the tertiary amines from the product. The former was converted by P_2O_5 into tetrahydroquinoline, the latter into julolidine:



Epichlorohydrin and diphenylamine similarly yield a tetrahydroquinoline:[3]



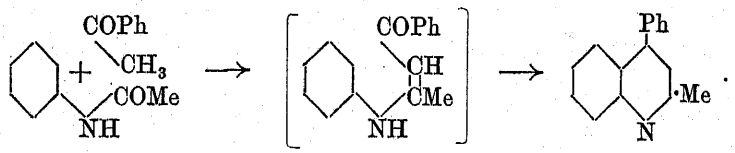
while from formanilide and dichlorohydrin Bamberger and Kitschelt[4] obtained after dehydration a mixture of quinoline, scatole and aniline:



[1] Pinkus, *Ber.*, 1892, **25**, 2801.
[2] *J. A. C. S.*, 1920, **42**, 1720.
[3] D.R.-P. 284291.
[4] *Ber.*, 1894, **27**, 3421.

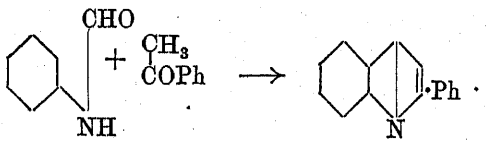
12. From acylanilines and acetophenone: $C_6\langle^{PhCO\cdot CH_3}_{NH—COR}$

Spallino and Salimei [1] synthesised 2-methyl-4-phenylquinoline by heating a mixture of acetanilide, acetophenone and zinc chloride at 250–300° for four days:

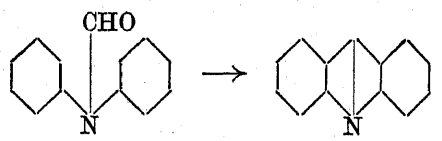


Benzanilide similarly at 200–230° gives 2 : 4-diphenylquinoline.

Formanilide [2] reacts quite differently with acetophenone, the product being not 4-phenyl- but 2-phenyl-quinoline. The process is similar to Bernthsen's acridine synthesis:

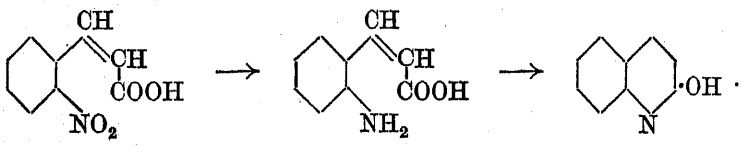


Cf.:



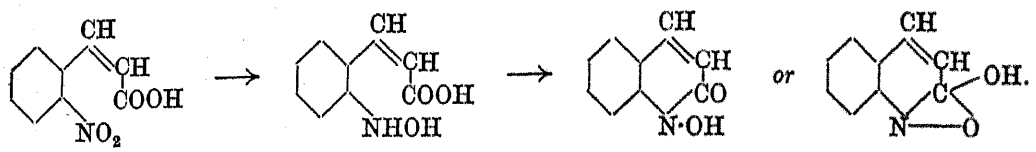
13. From *o*-nitrocinnamic acid etc.: $C_6\langle^{C=C}_{NO_2\ COOH}$

As early as 1852 Chiozza [3] reduced *o*-nitrocinnamic acid with NH_4SH and obtained carbostyril:

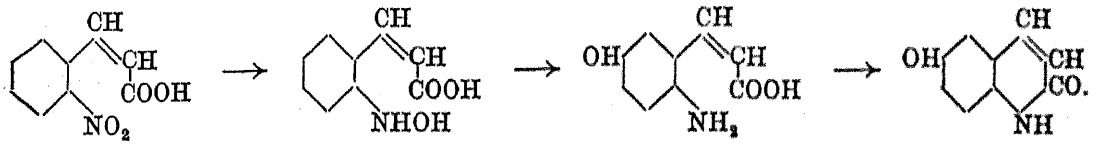


[1] *Gazz.*, 1912, **42**, 607. [2] Pictet and Barbier, *Bull. Soc. chim.*, 1895, [iii], **13**, 26.
[3] *Ann.*, 1852, **83**, 117.

Tiemann and Oppermann [1] used ferrous sulphate and baryta. With alcoholic ammonium sulphide there is formed in addition *N*-hydroxycarbostyril : [2]



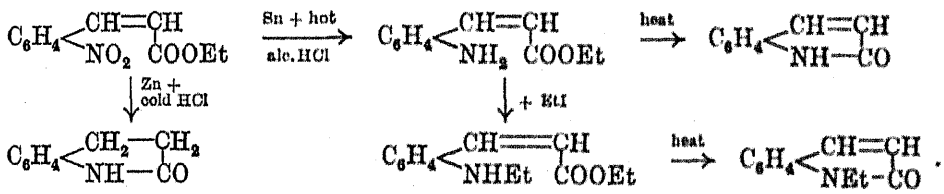
Electrolytic reduction in sulphuric acid gives 5-hydroxy-2-aminocinnamic acid, from which 6-hydroxycarbostyril is obtained by the action of conc. HCl at 160° : [3]



Stoermer and Heymann [4] showed that *ordinary* cinnamic acid (*i.e. trans*, m. p. 240°) gives by nitration and reduction a stable *o*-amino-derivative, whilst *allo*-cinnamic acid (*cis*, m. p. 143°) gives carbostyril directly.

o-Aminocinnamic acid may be prepared from *o*-chlorocinnamic acid by heating at 125–130° with ammonia in the presence of copper.[5] At a higher temperature, 160–170°, the product is carbostyril.

o-Nitrocinnamic *ester* was reduced to carbostyril by T. M. Morgan [6] and by Friedländer and Weinberg,[7] who also prepared the *N*-ethyl compound and dihydrocarbostyril :



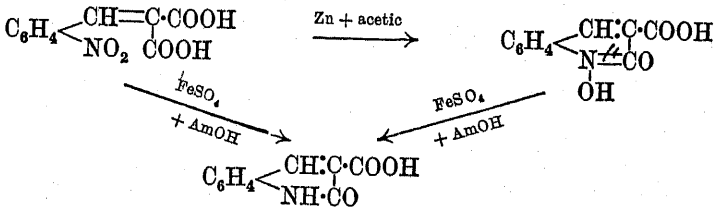
Decker [8] converted the two nitro-*o*-aminocinnamic acids into the corresponding nitrocarbostyrils.

α-Phenyl-*o*-nitrocinnamic acid reduced with sodium amalgam yields 3-phenylcarbostyril : [9]

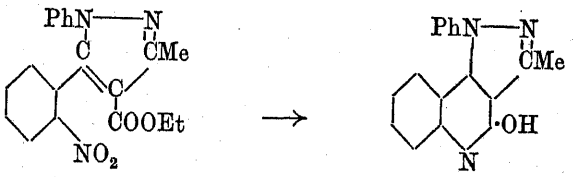


[1] *Ber.*, 1880, **13**, 2070.
[2] Friedländer and Ostermaier, *ibid.*, 1881, **14**, 1916; 1914, **47**, 3369; v. Niementowski, *ibid.*, 1907, **40**, 4293.
[3] Gattermann, *ibid.*, 1894, **27**, 1936; D.R.-P. 82445.
[4] *Ibid.*, 1912, **45**, 3099.
[5] H. Meyer and Beer, *Monatsh.*, 1913, **34**, 1173.
[6] *Chem. News*, 1877, **36**, 269.
[7] *Ber.*, 1882, **15**, 321, 1421, 2103.
[8] *J. pr. Chem.*, 1901, **64**, 85.
[9] Oglialoro and Rosini, *Gazz.*, 1890, **20**, 396.

The reduction of *o*-nitrobenzalmalonic acid has been studied by Stuart,[1] H. Meyer [2] and Heller and Wunderlich : [3]

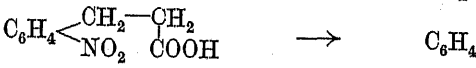


The pyrazole obtained from *o*-nitrobenzoylacetoacetic ester and phenylhydrazine behaves as an *o*-nitrocinnamic ester on reduction with $SnCl_2$: [4]

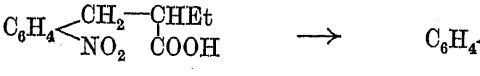


14. From *o*-nitrophenylpropionic acids etc : $C_6<^{CH_2-CHR}_{NO_2\ \ COOH}$

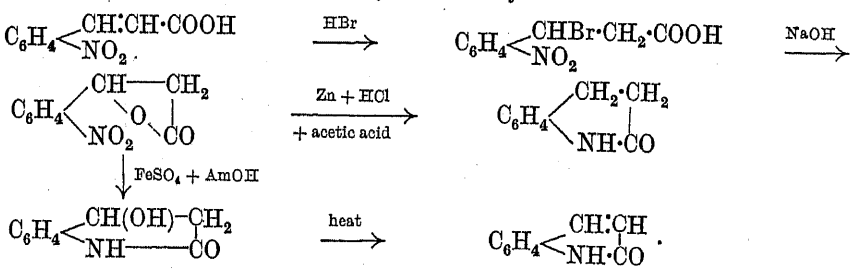
Dihydrocarbostyril results from the reduction of *β*-*o*-nitrophenylpropionic acid : [5]



The same compound was prepared by H. Meyer and Beer [6] by the action of ammonia and copper upon *o*-chlorodihydrocinnamic acid. Baeyer and Jackson [7] obtained 3-ethyldihydrocarbostyril from *β*-*o*-nitrophenyl-*α*-ethylpropionic acid :



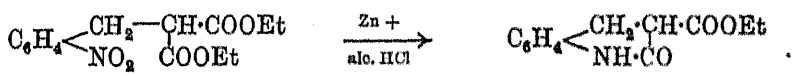
The hydrobromide of *o*-nitrocinnamic acid is converted by NaOH into a lactone which may be reduced to dihydrocarbostyril or to 4-hydroxydihydrocarbostyril.[8]



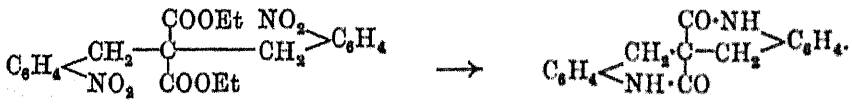
[1] *J. C. S.*, 1885, **47**, 155; 1888, **53**, 143.
[2] *Monatsh.*, 1908, **28**, 47.
[3] *Ber.*, 1914, **47**, 2889.
[4] Knorr and Jödicke, *ibid.*, 1885, **18**, 2262.
[5] Glaser and Buchanan, *Zeitschr. f. Chem.*, 1869, 164.
[6] *Monatsh.*, 1913, **34**, 1173.
[7] *Ber.*, 1880, **13**, 115.
[8] Einhorn, *ibid.*, 1883, **16**, 2212; 1884, **17**, 2011; D.R.-P. 28900.

The corresponding 6-chloro- and 6-methoxy-derivatives were obtained in a similar manner from 2-nitro-5-chlorocinnamic acid by Einhorn and Eichengrün.[1] The chlorine atom, being *para* to a nitro group, is readily replaced by ·OMe by the action of potassium methoxide.

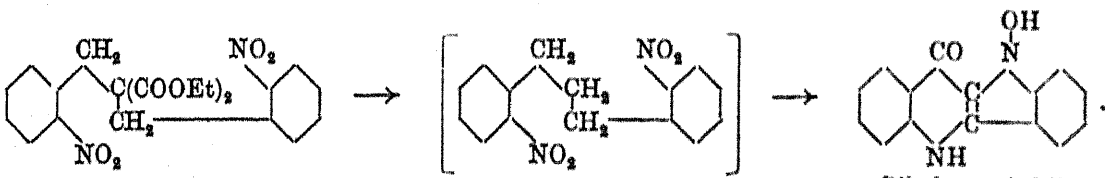
o-Nitrobenzylmalonic ester is also a source of dihydrocarbostyril derivatives :[2]



The *o* : *o'*-dinitrodibenzylmalonic ester gives two interesting compounds. By reduction it is converted into 3 : 3'-*bis*dihydrocarbostyrilspirane :[3]

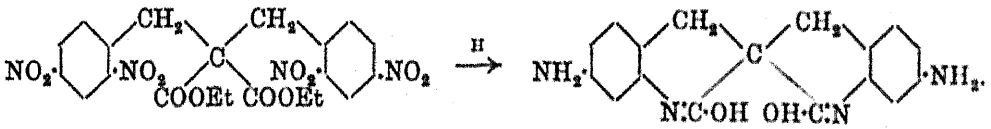


Warm caustic soda, on the other hand, hydrolyses off the two ·COOEt groups and by internal oxidation of the ·CH_2· groups at the expense of the ·NO_2 groups forms a quindoline derivative :[4]



Dihydroxyquindoline.

A similar double condensation, leading to a *spiro-bis*carbostyril, has recently been described by Radolescu :[5]

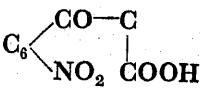


The product, though it contains no asymmetric atom, has been resolved by means of bromocamphorsulphonic acid. Possible only one of the carbonyl groups is enolised.

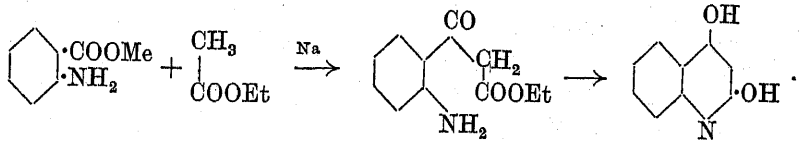
The anhydride of *o*-hydrazinodihydrocinnamic acid, namely, *N*-aminodihydrocarbostyril, is formed from the hydrazino-acid by the action of HCl :[6]



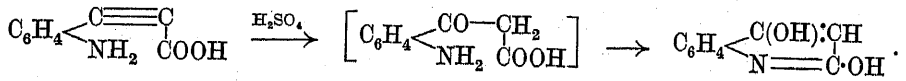
[1] *Ber.*, 1890, **23**, 1489; D.R.-P. 55119.
[2] Reissert, *ibid.*, 1896, **29**, 665; Leuchs and v. Katinsky, *ibid.*, 1922, **55**, 720.
[3] Lellmann and Schleich, *ibid.*, 1887, **20**, 437; Radolescu, *ibid.*, 1911, **44**, 1024; Leuchs and v. Katinsky, *ibid.*, 1922, **55**, 715, 718.
[4] Fichter and Boehringer, *ibid.*, 1906, **39**, 3932.
[5] *Zentr.*, 1923, iii, 139.
[6] Fischer and Kuzel, *Ann.*, 1883, **221**, 261.

15. From *o*-aminobenzoylacetic acid and its derivatives: 

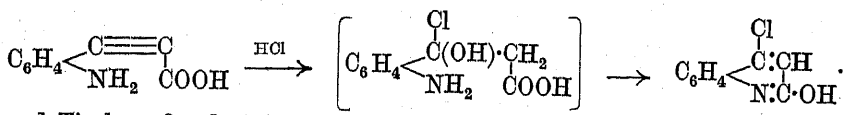
Erdmann [1] condensed anthranilic ester with acetic ester in the presence of sodium. The resulting *o*-aminobenzoylacetic ester was readily converted by heat into 2 : 4-dihydroxyquinoline :



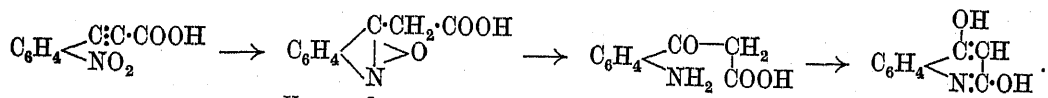
o-Aminobenzoylacetic acid is probably an intermediate in the hydrolysis of *o*-aminophenylpropiolic acid to 2 : 4-dihydroxyquinoline : [2]



When dilute HCl is used the product is 4-chlorocarbostyril :

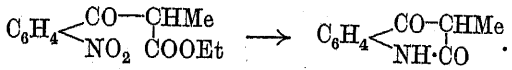


Heller and Tischner [3] reduced *o*-nitrophenylpropiolic acid by means of zinc and ammonium chloride to homoanthroxanic acid. This on further reduction with zinc and acetic acid gave *o*-aminobenzoylacetic acid and hence 2 : 4-dihydroxyquinoline :

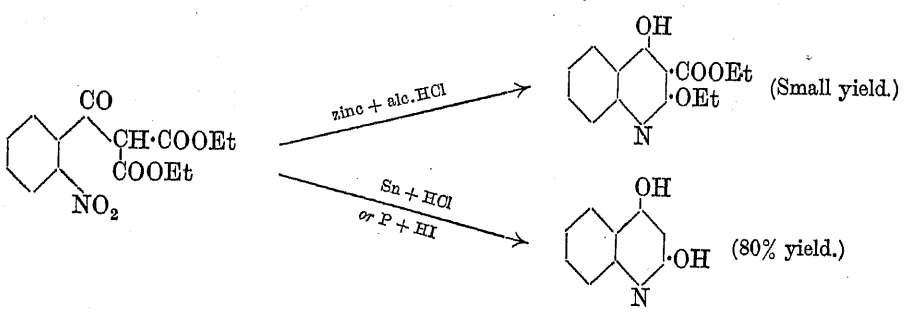


Homoanthroxanic acid.

α-o-Nitrobenzoylpropionic ester was reduced by Gabriel and Gerhard with HI and PH_4I : [4]

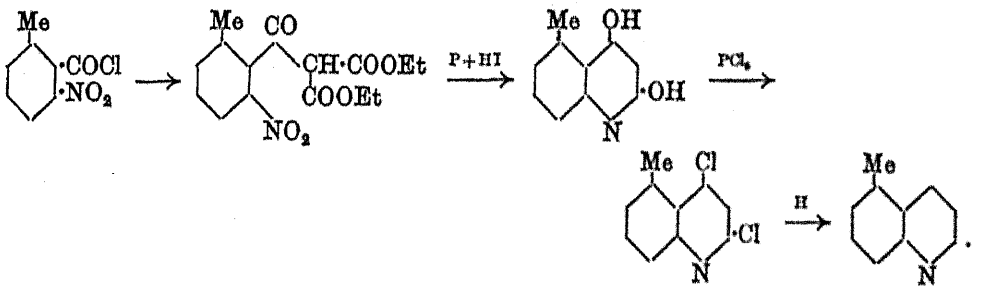


The reduction of *o*-nitrobenzoylmalonic ester has been described by Bischoff [5] and by Gabriel : [6]

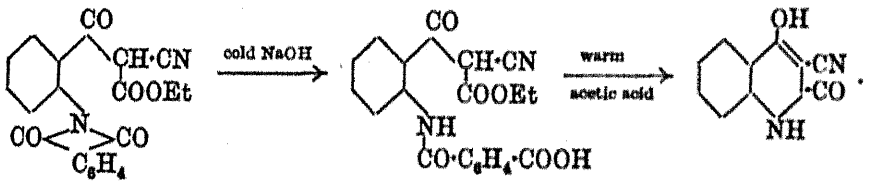


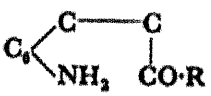
[1] *Ber.*, 1899, **32**, 3570. [2] Baeyer and Bloem, *ibid.*, 1882, **15**, 2147, 2151.
[3] *Ibid.*, 1909, **42**, 4555; see also Camps, *ibid.*, 1901, **34**, 2716. [4] *Ibid.*, 1921, **54**, 1070.
[5] *Ann.*, 1889, **251**, 360, 366, 376. [6] *Ber.*, 1918, **51**, 1500.

Gabriel and Thieme [1] used this method for the synthesis of 5-methylquinoline :



3-Cyano-2 : 4-dihydroxyquinoline was obtained by Gabriel [2] by the action of warm acetic acid upon the partial hydrolysis product from *o*-phthaliminobenzoylcyanacetic ester :



16. From β-*o*-nitrophenylated ketones : 

The reduction of *o*-nitrobenzylacetone gives tetrahydroquinaldine : [3]



Alber [4] obtained the corresponding 7-amino derivative from 2 : 4-dinitrobenzylacetone.

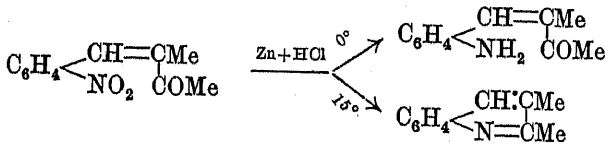
The reduction of *o*-nitrobenzalacetone [5] or its dibromide [6] yields quinaldine :



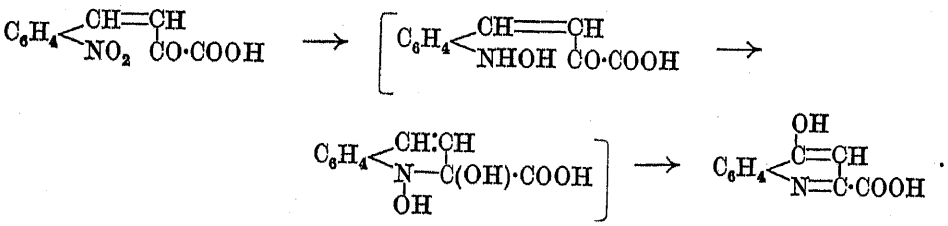
o-Nitrobenzalacetophenone similarly gives 2-phenylquinoline,[7] and from nitropiperonalacetone Haber [8] obtained 6 : 7-methylenedioxyquinaldine.

[1] *Ber.*, 1919, **52**, 1086.
[2] *Ibid.*, 1918, **51**, 1500.
[3] Jackson, *ibid.*, 1881, **14**, 889.
[4] *J. pr. Chem.*, 1904, **71**, 39.
[5] Drewson, *Ber.*, 1883, **16**, 1953; D.R.-P. 22138.
[6] Heller, *Ber.*, 1911, **44**, 2110.
[7] Goldschmidt, *ibid.*, 1895, **28**, 986.
[8] *Ibid.*, 1891, **24**, 623.

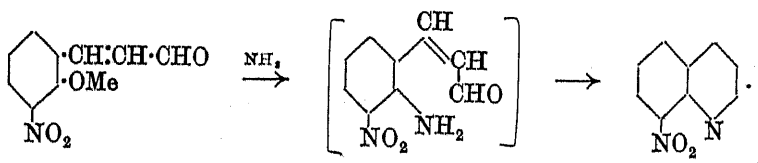
Heller, Lauth and Buchwaldt [1] find that reduction at 0° converts *o*-nitrobenzal-ethyl methyl ketone into the *o*-amino-compound, whilst at 15° the product is 2 : 3-dimethylquinoline :



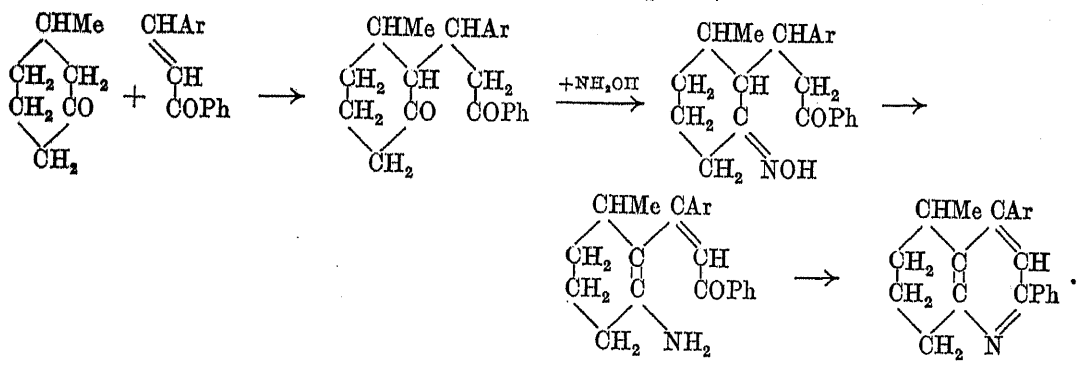
o-Nitrobenzalpyruvic acid is reduced by ferrous sulphate and ammonia to 4-hydroxy-quinaldinic acid : [2]



v. Miller and Kinkelin [3] prepared 8-nitroquinoline by the action of alcoholic ammonia upon 3-nitro-2-methoxycinnamic aldehyde :



With these reactions may be classed Stobbe's preparation of 5 : 6 : 7 : 8-tetrahydroquinolines by an extension of the Knoevenagel pyridine synthesis (p. 210) : [4]

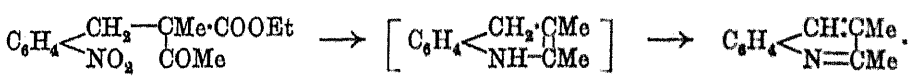


(Ar = ·C_6H_5, 3 : 4-$CH_2{<}^{O}_{O}{>}C_6H_3$·, *p*-MeO·C_6H_4·)

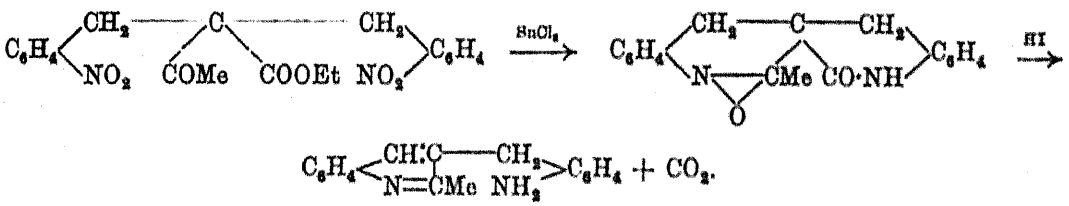
In these products the methyl group may be in position 5 or 7.

[1] *Ber.*, 1922, **55**, 483. [2] Heller, *ibid.*, 1910, **43**, 1923. [3] *Ibid.*, 1889, **22**, 1716.
[4] Stobbe, *ibid.*, 1902, **35**, 3978; *J. pr. Chem.*, 1912, **86**, 218; Rosenburg, *ibid.*, p. 250; Striegler, *ibid.*, p. 257; Cruikshanks, *ibid.*, p. 269.

The reduction of *o*-nitrobenzyl derivatives of β-keto-esters gives interesting results. The ketonic carbonyl reacts in preference to the ester group, which is easily hydrolysed off. Jaenisch [1] reduced *o*-nitrobenzyl-methylacetoacetic ester with P and HI, and obtained 2 : 3-dimethylquinoline (*not* the dihydro-compound) :



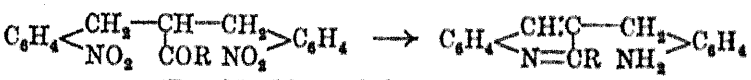
Gabriel and Wolter [2] obtained a *spiro*-compound by the reduction of the di-[nitrobenzyl]-derivative with $SnCl_2$ and HCl in acetic acid :



By "ketonic hydrolysis" the nitrobenzyl esters are converted into nitrobenzylacetones, which also give quinolines on reduction : [3]

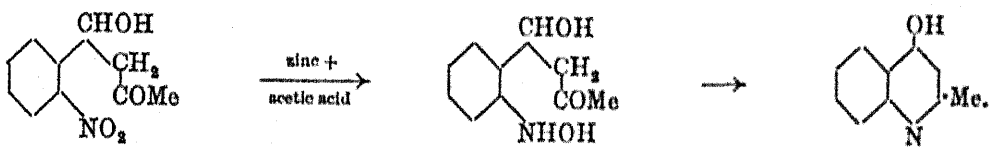


(Ar = Ph, *o*-MeO·C_6H_4.) (Jaenisch.)



(R = Me, Ph.) (Gabriel and Wolter.)

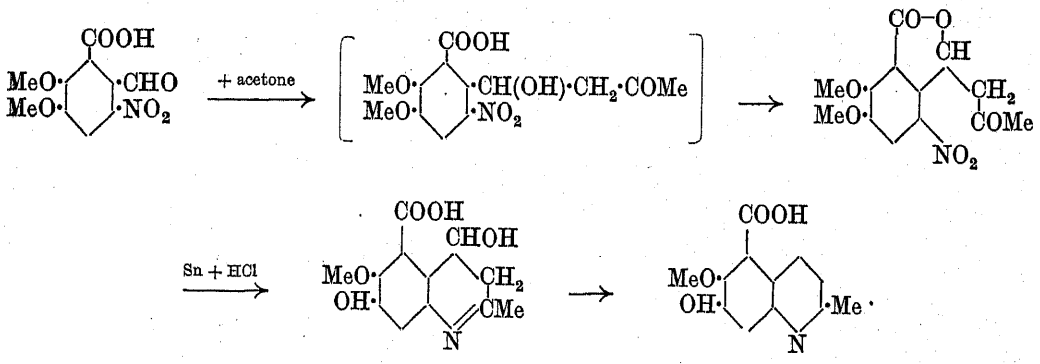
The so-called "lactic methyl ketones" obtained from *o*-nitrobenzaldehydes and acetone may also be converted into quinolines by reduction : [4]



2 : 4-Dinitrobenzaldehyde [5] and nitropiperonal [6] have similarly been condensed with acetone

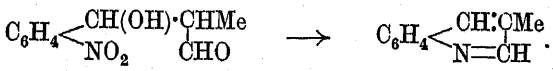
[1] *Ber.*, 1923, **56**, 2450. [2] *Ibid.*, p. 2445.
[3] Gabriel and Wolter, *loc. cit.*; Jaenisch, *loc. cit.*
[4] Heller and Sourlis, *Ber.*, 1908, **41**, 2692; D.R.-P. 89978.
[5] Braunholz, *J. C. S.*, 1922, **121**, 169.
[6] Herz, *Ber.*, 1905, **38**, 2855; Borsche and Quast, *ibid.*, 1919, **52**, 432.

and reduced to quinaldines or 4-hydroxyquinaldines. Book [1] has reduced the lactone obtained from nitro-opianic acid and acetone:

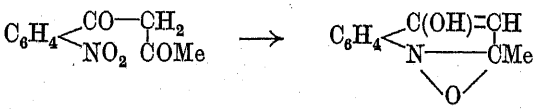


Nitropiperonalacetophenone [2] gives a 50% yield of the corresponding 6 : 7-methylenedioxy-2-phenylquinoline.

The condensation product of *o*-nitrobenzaldehyde and propionaldehyde is reduced to β-methylquinoline without production of the 4-hydroxy-derivative: [3]



o-Nitrobenzoylacetone is converted by $SnCl_2$ or by P and HI into a quinaldine derivative: [4]

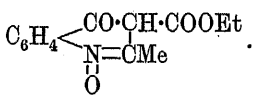


and similar ring-closure is observed with the *o*-nitrobenzoyl derivatives of cyanoacetophenone, acetophenone and benzoylacetic ester: [5]



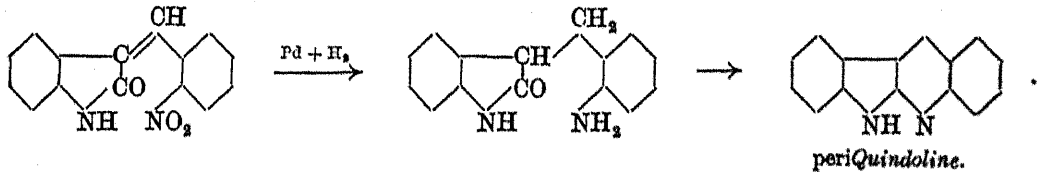
(R = ·CN, ·COOEt or ·H.)

In the case of acetophenone, as with acetone, the product is the oxido-compound, which must be further reduced to give the quinoline. McClusky,[6] who studied the reduction of *o*-nitrobenzoylacetoacetic ester, prefers for the oxido-compound the structure:

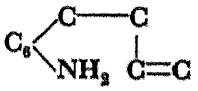


[1] *Ber.*, 1902, **35**, 1498; 1903, **36**, 2208.
[2] Borsche and Quast, *loc. cit.*
[3] Heller, *Ber.*, 1910, **43**, 1916.
[4] Gabriel and Gerhard, *ibid.*, 1921, **54**, 1071.
[5] *Idem, ibid.*, p. 1613.
[6] *J. A. C. S.*, 1922, **44**, 1575.

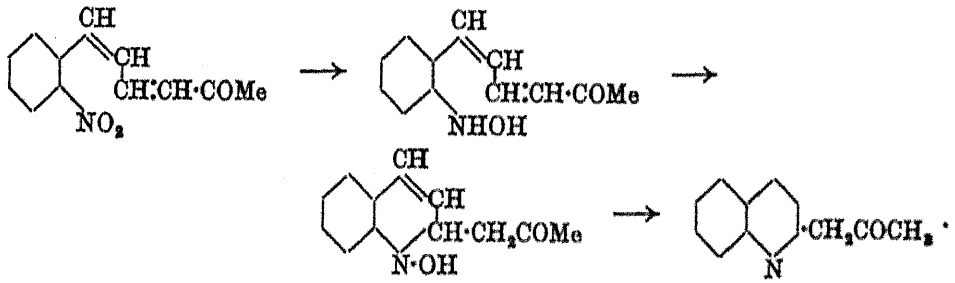
Mention may also be made of Kircher's synthesis of *peri*quindoline : [1]



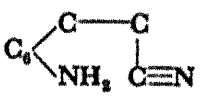
*peri*Quindoline.

17. From *o*-nitrocinnamylidene-acetone : 

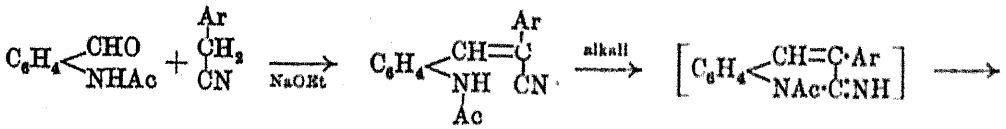
By reduction of the condensation product of *o*-nitrocinnamaldehyde with acetone Fischer and Kuzel [2] obtained acetonylquinoline :



Ring-closure occurs by addition at the double bond adjacent to the ketone group, probably by 1 : 4 addition and isomerisation of the enolic form so produced.

18. From derivatives of β-*o*-aminophenylpropionitrile : 

Ring-closure by addition of $\cdot NH_2$ at a $\cdot C{\equiv}N$ group occurs when certain *o*-nitro-nitriles are reduced or when the corresponding amines are liberated from their acyl derivatives. Thus Pschorr [3] prepared 2-amino-3-arylquinolines from acetyl-*o*-aminobenzaldehyde and arylaceto-nitriles :





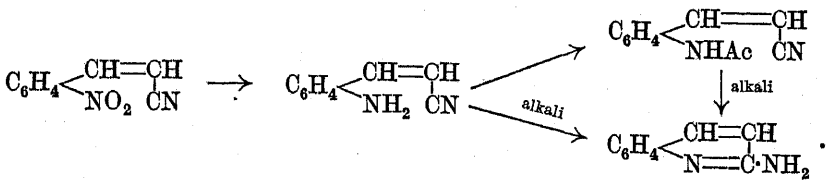
(Ar = Ph or *p*-$NO_2{\cdot}C_6H_4$.)

The acetyl group is transferred during the reaction from the less basic to the more strongly basic group, and by prolonged action of the cold alkali or by warming at 100° it may be removed

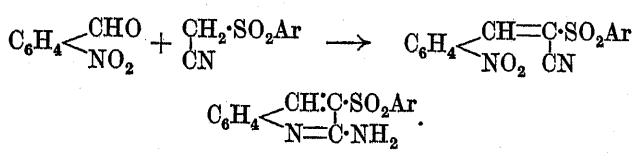
[1] *Nachr. K. Ges. Wiss. Göttingen*, 1921, 154. [2] *Ber.*, 1883, **16**, 163. [3] *Ibid.*, 1898, **31**, 1289.

altogether. The intermediate amino-nitrile is isolable in the case of the *p*-nitrophenyl compound, but benzyl cyanide gives 2-amino-3-phenylquinoline directly.

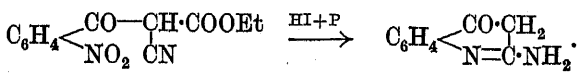
Acetonitrile itself fails to react with acetyl-*o*-aminobenzaldehyde, but its *o*-nitrobenzal derivative may be reduced, acetylated and then converted into an aminoquinoline :



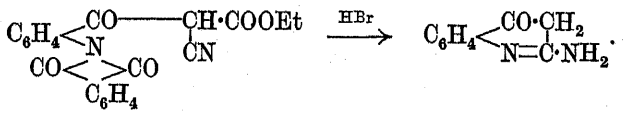
Similarly, the arylsulphonyl derivatives of acetonitrile have been condensed with *o*-nitrobenzaldehyde and reduced to *α*-amino-*β*-arylsulphonylquinolines by Tröger and Köppen-Kastrop : [1]



The reduction of *o*-nitrobenzoylcyanacetic ester with HI and phosphorus yields 2-amino-4-hydroxyquinoline, the ester group being hydrolysed off : [2]

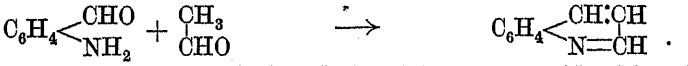


The same product is obtained from *o*-phthaliminobenzoylcyanacetic ester by hydrolysis :



19. From *o*-aminobenzaldehydes : $C_6<^{CHO}_{NH_2} + ^{CH_2\cdot R}_{CO\cdot R}$

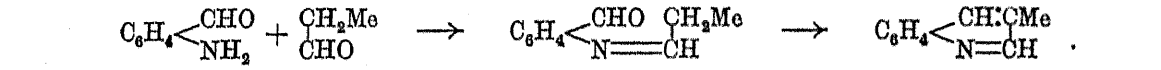
This important synthesis was discovered in 1882 by Friedländer,[3] who condensed *o*-aminobenzaldehyde with acetaldehyde in the presence of a trace of NaOH at 40–50° :



The reaction appears to be quite general, though the yields vary considerably. Propionaldehyde gives very little *β*-methylquinoline by Friedländer's method,[4] but by slowly heating *o*-aminobenzaldehyde with propionaldehyde alone to 220° Wislicenus and Elvert [5] obtained 80–85%

[1] *J. pr. Chem.*, 1922, **104**, 335. [2] Gabriel, *Ber.*, 1918, **51**, 1500. [3] *Ibid.*, 1882, **15**, 2572.
[4] Koenigs and Bischkopf, *ibid.*, 1901, **34**, 4330. [5] *Ibid.*, 1909, **42**, 1144.

yield of the β-methylquinoline. In the presence of 1% KOH the main product is the oily propylideneaminobenzaldehyde, which may be converted into the quinoline by distillation:



Good yields were obtained by a similar method from butyraldehyde and œnanthaldehyde.[1]

Ketones give better results than aldehydes with NaOH. Acetone yields quinaldine and acetophenone 2-phenylquinoline.[2] In the case of ketones of the type $MeCO{\cdot}CH_2R$, the methyl group takes the α-position in the resulting quinoline. Thus methyl ethyl ketone [3] gives only 2 : 3-dimethylquinoline and no 2-ethylquinoline:



R and R′ may also be negative groups. Chloroacetone (R = Me, R′ = Cl) yields 3-hydroxyquinaldine, the Cl being hydrolysed to ·OH.[4] β-Nitroquinolines may be obtained from methazonic acid, NOH:CH·CH:NOOH, which reacts as the oxime of nitroacetaldehyde.[5] (R = H, R′ = NO_2.) Tröger [6] has recently prepared a series of β-arylsulphonylquinolines:



(Ar = Ph, *p*-C_7H_7·, *p*-ClC_6H_4· or β-$C_{10}H_7$·; R = Me, Ph, ·OH.)

Acids or esters which contain a sufficiently reactive $\cdot CH_2{\cdot}CO\cdot$ grouping may also be used. Acetoacetic ester yields quinaldine-3-carboxylic ester.[6] Benzoylacetic ester, malonic acid (*not* the ester) and succinic anhydride give the corresponding quinoline derivatives.

In certain cases, piperidine is a better condensing agent than NaOH.[7] From acetylacetone, *o*-aminobenzaldehyde and a trace of piperidine Stark obtained a 92% yield of 3-acetylquinaldine.

An unexpected result is the formation of 3-benzoylquinaldine rather than 3-acetyl-2-phenylquinoline by condensation of aminobenzaldehyde with benzoylacetone: [8]



The reaction fails with desoxybenzoin, dihydroxyacetophenone, glucose and lævulic acid.[9]

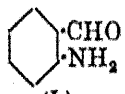
Geigy and Koenigs,[10] using *o*-aminobenzophenone in place of aminobenzaldehyde, obtained only traces of 4-phenylquinoline with acetaldehyde, but with acetone and conc. NaOH they were able to prepare 4-phenylquinaldine:

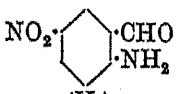


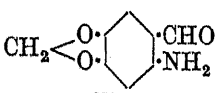
[1] v. Braun, Petzold and Seemann, *Ber.*, 1922, **55**, 3785.
[2] Friedländer and Göhring, *ibid.*, 1883, **16**, 1835; Eliasberg and Friedländer, *ibid.*, 1892, **25**, 1752.
[3] Eliasberg and Friedländer, *loc. cit.*; Fränkel, *Diss. Freiburg*, 1896; Koenigs and Bischkopf, *loc. cit.*
[4] Koenigs and Stockhausen, *Ber.*, 1902, **35**, 2554. [5] *J. pr. Chem.*, 1922, **103**, 193; **104**, 335.
[6] Friedländer and Göhring, *Ber.*, 1883, **16**, 1835; Eliasberg and Friedländer, *loc. cit.*; Claus and Steinitz, *Ann.*, 1894, **282**, 115; Koenigs and Bischkopf, *loc. cit.*
[7] Stark, *Ber.*, 1907, **40**, 3427; Stark and Hoffmann, *ibid.*, 1909, **42**, 715. [8] *Idem, loc. cit.*
[9] Tröger and Menzel, *J. pr. Chem.*, 1921, **103**, 188. [10] *Ber.*, 1885, **18**, 2405.

The condensation of *o*-aminobenzophenone and methazonic acid gives 3-nitro-4-methylquinoline.[1]

Although Friedländer's synthesis has been applied to a variety of aldehydes, ketones, etc., the choice of *o*-aminobenzaldehyde derivatives is very limited, only four having so far been employed :


(I.)


(II.)


(III.)


(IV.)

The following condensations have been described (the α- and β-substituents in the resulting quinolines are indicated) :

(a) *With o-aminobenzaldehyde* (I) :

Aldehyde, ketone, etc.	α	β	*References.*
Acetaldehyde.	H	H	1, 4, 6
Methazonic acid.	H	NO_2	20
Propionaldehyde.	H	Me	11, 17, 34
Butyraldehyde.	H	Et	30
Œnanthaldehyde.	H	C_5H_{11}	30
Phenylacetaldehyde.	H	Ph	30
Glucose.	fails.		26
Acetone.	Me	H	2, 4, 6
*iso*Nitrosoacetone.	CH:NOH	H	
Chloroacetone.	Me	OH	12
Acetonesulphonic acid.	Me	$\cdot SO_2H$	21
Arylsulphonylacetones.	Me	$\cdot SO_2Ar$	25
Diarylsulphonylacetones.	CH_2SO_2Ar	$\cdot SO_2Ar$	33
Phthaliminoacetone.	Me	NH_2	31
Methyl ethyl ketone.	Me	Me	6, 10, 11
Diethyl ketone.	Et	Me	6
Methyl hydroxy*iso*propyl ketone.	CMe_2OH	H	29
Acetophenone.	Ph	H	2, 6
Phthaliminoacetophenone.	Ph	NH_2	31
Bromoacetophenone.	Ph	$\cdot OH$	31
Dihydroxyacetophenone.	fails.		25
Arylsulphonylacetophenones.	Ph	$\cdot SO_2Ar$	26, 33
Anisyl chloromethyl ketone.	$MeOC_6H_4$	OH	31
β-Naphthyl methyl ketone.	$C_{10}H_7$	H	6
Benzalacetone.	$PhCH:CH\cdot$	H	18
Acetylacetone.	Me	COMe	6, 15, 16
Benzoylacetone.	Me	COPh	16
Dibenzoylmethane.	Ph	COPh	16
Desoxybenzoin.	fails.		25
Acetoacetic ester.	Me	COOEt	2, 6, 7, 11
Benzoylacetic ester.	Ph	COOEt	2
Arylsulphonylacetic esters.	OH	SO_2Ar	26
Arylsulphonylacetamides.	OH	SO_2Ar	26
Malonic acid.	OH	COOH	2
Succinic anhydride.	OH	CH_2COOH	19
Lævulic acid.	fails.		
α-Acetylpyrrole.	$-C_4H_4N$	H	23
α-Acetylpyridine.	$-C_5H_5N$	H	23

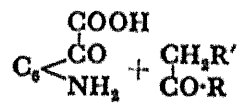
[1] D.R.-P. 335197.

Aldehyde, ketone etc.	α	β	*References*
Diacetyl (double). α-Acetylquinoline.	$-C_9H_6N$	H	23
β-Quinolinylacetaldehyde.	$-C_9H_6N$	H	5, 8
γ-Acetoacetylquinoline. (Acetyl group is hydrolysed off.)	$-C_9H_6N$	H	9
(b) *With 5-nitro-2-aminobenzaldehyde* (II):			
Acetone.	Me	H	13
(c) *With aminopiperonal* (III):			
Acetaldehyde.	fails.		24
Acetone.	Me	H	14, 22
Phthaliminoacetone.	Me	NH_2	32
Methyl ethyl ketone.	Me	Me	22
Acetophenone.	Ph	H	22
Phthaliminoacetophenone.	Ph	NH_2	32
α-Hydrindone. β-Hydrindone. α : γ-Diketohydrindone.	(Indoquinolines.)		28
(d) *With aminoveratraldehyde* (IV):			
Acetone.	Me	H	27
Methyl ethyl ketone.	Me	Me	27
Acetophenone.	Ph	H	27

References.

[1] Friedländer, *Ber.*, 1882, **15**, 2572. [2] Friedländer and Göhring, *ibid.*, 1883, **16**, 1835. [3] *Idem*, *ibid.*, 1884, **17**, 459. [4] Anon., *Dingl. polyt. J.*, 1884, **250**, 533. [5] Carlier and Einhorn, *Ber.*, 1890, **23**, 2894. [6] Eliasberg and Friedländer, *ibid.*, 1892, **25**, 1752. [7] Claus and Steinitz, *Ann.*, 1894, **282**, 115. [8] Einhorn and Sherman, *ibid.*, 1895, **287**, 42. [9] Weidel, *Monatsh.*, 1896, **17**, 401. [10] Fränkel, *Diss. Freiburg*, 1896 (*J. C. S.*, Abstr., 1897, i, 487). [11] Koenigs and Bischkopf, *Ber.*, 1901, **34**, 4330. [12] Koenigs and Stockhausen, *ibid.*, 1902, **35**, 2554; Pfitzinger, *J. pr. Chem.*, 1902, **66**, 263. [13] Cohn and Springer, *Monatsh.*, 1903, **24**, 87. [14] Herz, *Ber.*, 1905, **38**, 2855. [15] Stark, *ibid.*, 1907, **40**, 3427. [16] Stark and Hoffmann, *ibid.*, 1909, **42**, 715. [17] Wislicenus and Elvert, *ibid.*, p. 1144. [18] v. Ismailsky, *J. pr. Chem.*, 1911, **85**, 90. [19] Perkin and Robinson, *J. C. S.*, 1913, **103**, 1980. [20] D.R.-P. 335197. [21] Beathorn and Geisselbrecht, *Ber.*, 1920, **53**, 1026. [22] Rilliet and Kreitmann, *Helv. Chim. Acta*, 1921, **4**, 596. [23] Smirnoff, *ibid.*, p. 806. [24] Sonn and Benirschke, *Ber.*, 1921, **54**, 1736. [25] Tröger and Menzel, *J. pr. Chem.*, 1921, **103**, 193–215. [26] Tröger and Köppen-Kastrop, *ibid.*, 1922, **104**, 335–367. [27] Rilliet, *Helv. Chim. Acta*, 1922, **5**, 550. [28] Armit and Robinson, *J. C. S.*, 1922, **121**, 832. [29] Scheibler and Fischer, *Ber.*, 1922, **55**, 2920. [30] v. Braun, Petzold and Seemann, *ibid.*, p. 3785. [31] Bargellini and Berlingozzi, *Gazz.*, 1923, **53**, i, 3–11. [32] Berlingozzi, *R. A. L.*, 1923, [v], **32**, i, 339. [33] Tröger and v. Seelen, *J. pr. Chem.*, 1923, **105**, 208–231. [34] v. Braun, Gmelin and Schultheiss, *Ber.*, 1923, **56**, 1342.

20. From isatic acid and ketones etc.:



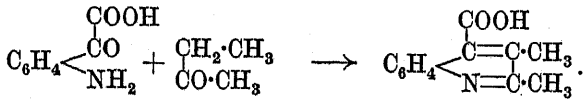
Just as pyruvic acid may be substituted for acetaldehyde in Döbner's synthesis, so Pfitzinger [1] substituted isatic acid (I) for the *o*-aminobenzaldehyde used by Friedländer:



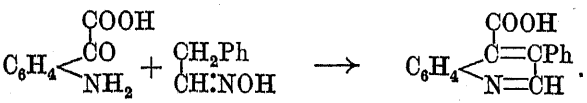
(I.) *Aniluvitonic acid.*

[1] *J. pr. Chem.*, 1886, **33**, 100.

The method remained undeveloped until eleven years later (when isatin from synthetic indigo became available). It was then applied by Pfitzinger and others to a large number of ketones. As in Friedländer's synthesis, the quinolines from unsymmetrical ketones usually contain the *smaller* group in the α-position. Thus methyl ethyl ketone gives 2 : 3-dimethylcinchoninic acid rather than the 2-ethyl derivative *: [1]



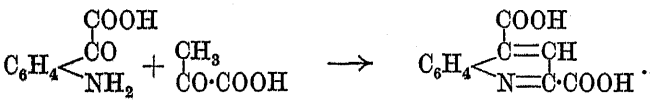
The isatic acid is prepared by boiling isatin with conc. NaOH and is used directly without isolation. The presence of so much alkali causes resinification when aldehydes are used instead of ketones, and even with acetone Pfitzinger [2] found it advisable to work with the *iso*nitroso derivative. This suggested the employment of aldoximes in place of aldehydes : [3]



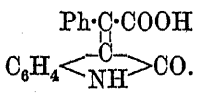
(65% yield.)

Isatin-β-oxime is formed as by-product.

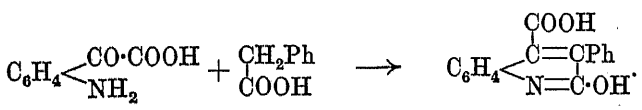
Keto-acids or -esters condense with isatic acid to give carboxylated cinchoninic acids. For example, pyruvic acid yields quinoline -2 : 4-dicarboxylic acid : [4]



Gysae [5] by heating together isatin, phenylacetic acid and sodium acetate, obtained " isaphenic acid," to which he gave the structure :

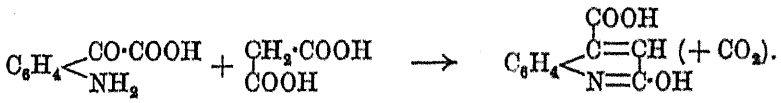


Borsche and Jacobs [6] showed, however, that the compound is really a quinoline derivative, identical with that prepared by Hübner [7] from isatin and phenylacetic anhydride :

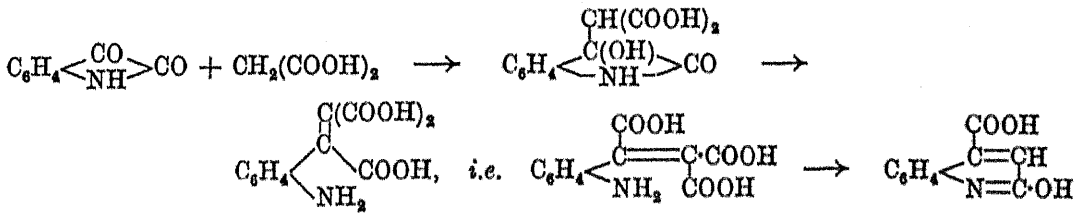


[1] Pfitzinger, *J. pr. Chem.*, 1897, **56**, 283. [2] *Ibid.*, 1902, **66**, 263.
[3] Pfitzinger, *loc. cit.*; Hübner, *Ber.*, 1906, **39**, 983. [4] Pfitzinger, *loc. cit.*
[5] *Ber.*, 1893, **26**, 2483. [6] *Ibid.*, 1914, **47**, 354. [7] *Ibid.*, 1908, **41**, 486.
* 2-Ethylcinchoninic acid has, however, been isolated from the product by v. Braun, Gmelin and Schultheiss (*ibid.*, 1923, **56**, 1344).

Borsche and Jacobs also condensed isatin with malonic acid :

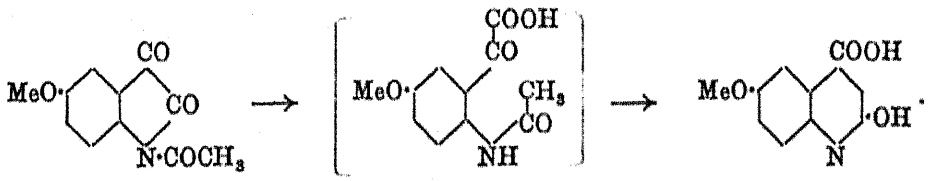


The mechanism they suggest is as follows :

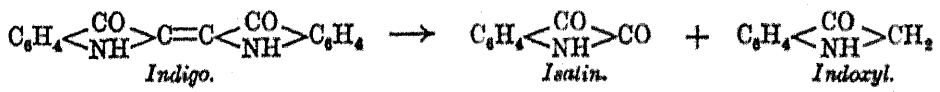


(see, however, footnote on p. 291).

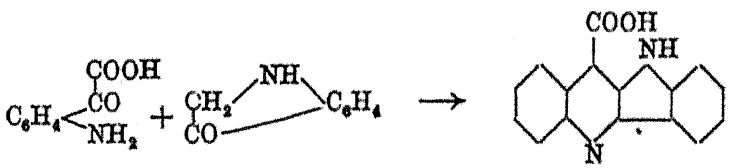
Halberkann [1] obtained 6-methoxycarbostyril-4-carboxylic acid by warming 5-methoxy-acetylisatin with NaOH :



In connection with Pfitzinger's synthesis may be mentioned the formation of " flavindin " by the over-reduction of indigo.[2] The constitution of this product was shown by Fichter and Rohner [3] to be that of quindoline-5-carboxylic acid. Flavindin was synthesised independently by Noelting and Steuer [4] from isatin and indoxyl. The method of formation from indigo is thus an example of Pfitzinger's synthesis :



Indigo. *Isatin.* *Indoxyl.*

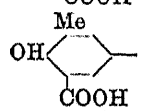
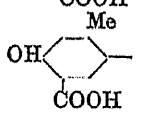
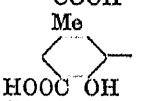
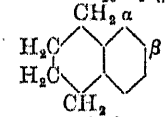
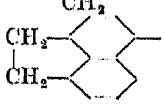


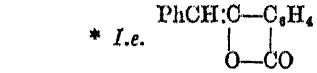
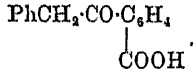
Flavindin.
(Quindoline-5-carboxylic acid.)

[1] *Ber.*, 1921, **54**, 3090.
[2] Schutzenberger, *Compt. rend.*, 1877, **85**, 147; Giraud, *ibid.*, 1880, **90**, 1429.
[3] *Ber.*, 1910, **43**, 3489. [4] *Ibid.*, p. 3512.

The following quinolines have been prepared by Pfitzinger's method:

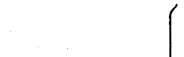
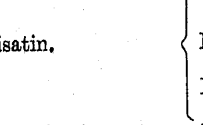
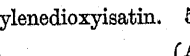
(a) *From isatin or isatic acid:*

Ketone etc.	*Substituents in the resulting cinchoninic acid.* α-	β-	*References.*
Acetaldehyde.		(failed).	2
Acetaldoxime.	H	H	4
Methazonic acid.	H	NO_2	22
Propaldoxime.	H	Me	6
Butyraldoxime.	H	Et	7
Phenylacetaldoxime.	H	Ph	5
Acetone.	Me	H	1, 2, 17
*iso*Nitrosoacetone.	·CH:NOH	H	4
Methyl ethyl ketone.	Me	Me	2, 33
	H	Et	33
Acetophenone.	Ph	H	2, 3, 17
m-Aminoacetophenone. / Acetyl-*m*-aminoacetophenone.	$NH_2 \cdot C_6H_4$	H	16 / 14
p-Iodoacetophenone.	$I \cdot C_6H_4$	H	15
o-, *m*-, and *p*-Hydroxyacetophenones.	$OH \cdot C_6H_4$	H	12
5-Acetosalicylic acid.		H	18, 20
5-Aceto-*o*-cresotic acid.		H	19
5-Aceto-*m*-cresotic acid.		H	19
3-Aceto-*p*-cresotic acid.		H	19
Phenacylamine.	Ph	$\cdot NH_2$	14, 16
Phenacyl bromide.	Ph	·OH	32
p-Methoxyphenacyl chloride.	$MeO \cdot C_6H_4$	·OH	32
Desoxybenzoin.	Ph	Ph	2
Dibenzyl ketone.	$PhCH_2$·	Ph	3
Benzyl *p*-tolyl ketone.	$Me \cdot C_6H_4$·	Ph	10, 17
Benzyl *p*-anisyl ketone.	$MeO \cdot C_6H_4$	Ph	16, 17
Benzalphthalide.*	$o\text{-}COOH \cdot C_6H_4$	Ph	10
Methyl α-naphthyl ketone.	$\alpha\text{-}C_{10}H_7$	H	11
Methyl β-naphthyl ketone.	$\beta\text{-}C_{10}H_7$	H	11
2-Acetyl-1-naphthol.	$\alpha\text{-}OH \cdot C_{10}H_6\text{-}(\beta)$	H	11
Methyl α-tetralyl ketone. / Methyl β-tetralyl ketone.		H / H	24 / 30, 36
Methyl 5-acenaphthyl ketone.		H	31

* *I.e.*  reacting as  .

Ketone etc.	*Substituents in the resulting cinchoninic acid.* α-	β-	*References.*
α-Acetylfurane.	α-C_4H_3O	H	29
α-Acetylpyrrole.	α-C_4H_3NH·	H	29
α-Acetylthiophene.	α-C_4H_3S·	H	25
Phenylacetic acid.	·OH	Ph	8, 23
Pyruvic acid.	·COOH	H	2
Malonic acid.	·OH	·COOH	9
Acetoacetic ester.	Me	·COOH	2, 3
Benzoylacetic ester.	Ph	·COOH	3
Lævulic acid.	Me	·CH_2COOH	3
Acetonedicarboxylic ester.	·CH_2COOH	(·COOH)	3
Oxalacetic ester.		(failed).	3
*cyclo*Pentanone.			9, 34
*cyclo*Hexanone.	Products of the hydrogenated acridine type.		9, 17, 34
3- and 4-Methyl*cyclo*hexanones.			9
Pulegone.			9
*cyclo*Heptanone.			9

(b) *From substituted isatins or isatic acids :*

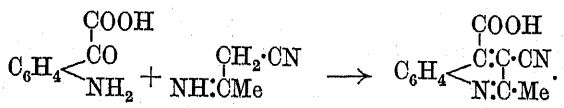
Isatin.	*Ketone etc.*	Py-*substituents in resulting cinchoninic acid.* α-	β-	*References.*
5-Methylisatin.	Acetone.	Me	H	2
	5-Acetosalicylic acid.		H	21
	3-Aceto-*p*-cresotic acid.		H	21
	Desoxybenzoin.	Ph	Ph	10
	Methyl β-naphthyl ketone.	β-$C_{10}H_7$	H	11
	Acetoacetic ester.	Me	·COOH	3
5 : 7-Dimethylisatin.	Acetaldoxime.		(failed).	26
	Desoxybenzoin.	Ph	Ph	10
	Benzyl *p*-tolyl ketone.	Me·C_6H_4·	Ph	10
5-Methoxyisatin	Acetaldoxime.	H	H	28
	Acetone.	Me	H	28
	Acetophenone.	Ph	H	28
	Desoxybenzoin.	Ph	Ph	28
	α-Acetylfurane.	α-C_4H_3O·	H	28
	(Acetic acid.)	·OH	H	28
	Pyruvic acid.	·COOH	H	28
	Oxalacetic ester.	·COOH	·COOH	28
5-Bromoisatin.	5-Acetosalicylic acid.		H	21
	Methyl α-tetralyl ketone.		H	24
	Methyl β-tetralyl ketone.		H	36
5 : 7-Dibromoisatin.	Desoxybenzoin.	Ph	Ph	10
5-Nitroisatin.	Acetophenone.	Ph	H	14
4-Carboxyisatin.	Acetophenone.	Ph	H	35
5 : 6-Methylenedioxyisatin.	5-Acetosalicylic acid.		H	21
Methylene-5 : 5′-di-isatin.	Acetone.	Me	H	27
	Acetophenone.	Ph	H	27
	*cyclo*Hexanone.	·$CH_2CH_2CH_2CH_2$·		27

References.

[1] Pfitzinger, *J. pr. Chem.*, 1886, **33**, 100. [2] *Idem, ibid.*, 1897, **56**, 283–320. [3] Engelhard, *ibid.*, 1898, **57**, 467. [4] Pfitzinger, *ibid.*, 1902, **66**, 263. [5] Hübner, *Ber.*, 1906, **39**, 982. [6] Ornstein, *Dissn. Berlin*, 1904; *Ber.*, 1907, **40**, 1088. [7] Mulert, *Dissn. Berlin*, 1906; *Ber.*, 1906, **39**, 1904. [8] Hübner, *ibid.*, 1908, **41**, 482. [9] Borsche, *Ann.*, 1910, **377**, 120, 122; Borsche and Jacobs, *Ber.*, 1914, **47**, 354. [10] D.R.-P. 249765. [11] D.R.-P. 284232. [12] D.R.-P. 284233. [13] D.R.-P. 287304. [14] D.R.-P. 287804. [15] D.R.-P. 288303. [16] D.R.-P. 288865. [17] D.R.-P. 290703. [18] D.R.-P. 293467. [19] D.R.-P. 293905. [20] D.R.-P. 303681. [21] D.R.-P. 305885. [22] D.R.-P. 335197. [23] D.R.-P. 343322. [24] D.R.-P. 344027. [25] Hartmann and Wybert, *Helv. Chim. Acta*, 1919, **2**, 60–63. [26] Späth, *Monatsh.*, 1919, **40**, 93–128. [27] Borsche and Meyer, *Ber.*, 1921, **54**, 2841. [28] Halberkann, *ibid.*, pp. 3090–3107. [29] Ciusa, *Gazz.*, 1922, **52**, ii, 47. [30] v. Braun, Hahn and Seemann, *Ber.*, 1922, **55**, 1687. [31] v. Braun and Wolff, *ibid.*, p. 3675. [32] Bargellini and Berlingozzi, *Gazz.*, 1923, **53**, i, 3. [33] v. Braun, Gmelin and Schultheiss, *Ber.*, 1923, **56**, 1344. [34] v. Braun, Petzold and Schultheiss, *ibid.*, p. 1349. [35] v. Braun and Hahn, *ibid.*, p. 2345. [36] D.Pat.Anm. C. 29461. [37] D.Pat.Anm. N. 16994.

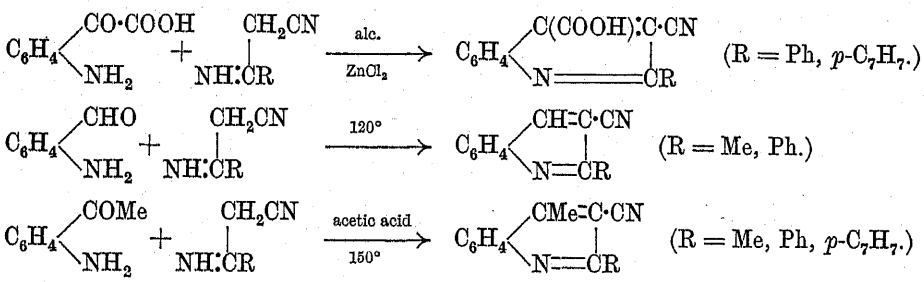
21. From o-aminobenzaldehyde etc. and dinitriles: $C_6\langle^{CO}_{NH_2} + {}^{CH_2CN}_{NH{:}CR}$

This modification of the Friedländer and Pfitzinger methods consists in the use of dinitriles, $NH{:}CR{\cdot}CH_2{\cdot}CN$, in place of ketones. Walther [1] condensed isatic acid with acetodinitrile and obtained 2-methyl-3-cyanocinchoninic acid:



When isatin itself is used the product is a pyridine derivative * (see p. 208).

Walther's method was extended by E. v. Meyer [2] to other dinitriles and to o-aminoacetophenone:



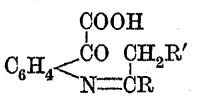
(R = Ph, p-C_7H_7.)

(R = Me, Ph.)

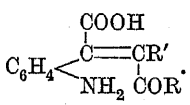
(R = Me, Ph, p-C_7H_7.)

[1] *J. pr. Chem.*, 1903, **67**, 504. [2] *Ibid.*, 1914, **90**, 1–52.

* The formation of a pyridine from isatin and a quinoline from isatic acid indicates that in Pfitzinger's synthesis the intermediate compounds are of type (I) rather than type (II), as suggested by Borsche and Jacobs (p. 288):



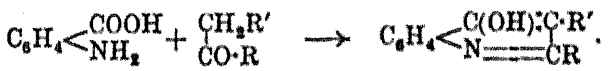
(I.)



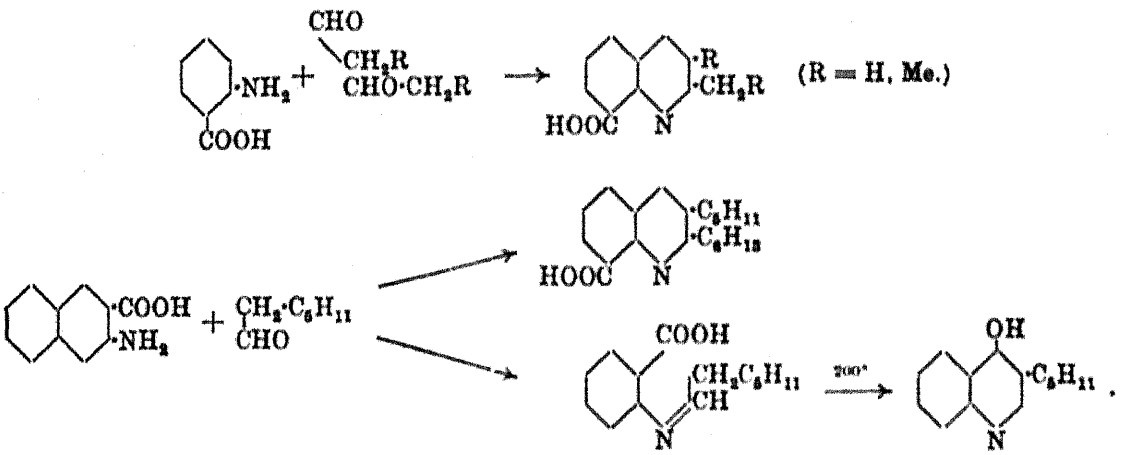
(II.)

22. From anthranilic acid and ketones etc.: 

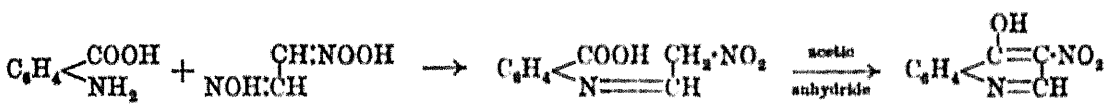
This method, due to v. Niementowski,[1] is a further extension of Friedländer's synthesis, *o*-aminobenzoic acid being used in place of the corresponding aldehyde :



Aldehydes react in two ways with anthranilic acid, the main product being a quinoline-8-carboxylic acid formed by the Döbner–Miller reaction (p. 251). Acetaldehyde, chloral and propionaldehyde give only Schiff bases and the Döbner–Miller products; from œnanthaldehyde, however, some 10% of 3-amyl-4-hydroxyquinoline is obtained :[2]

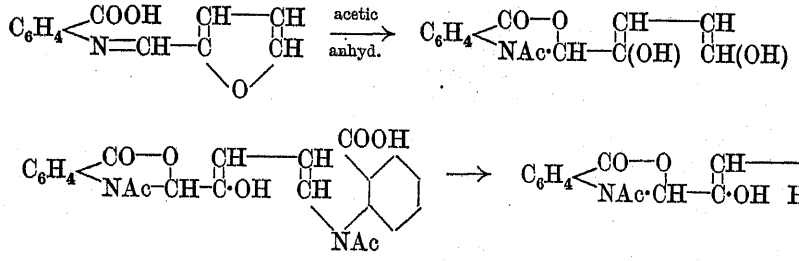


Methazonic acid, NOH:CH·CH:NOOH, reacts normally with *o*-amino-acids, yielding first an anil and then, by heating with acetic anhydride, a 3-nitro-4-hydroxyquinoline :[3]

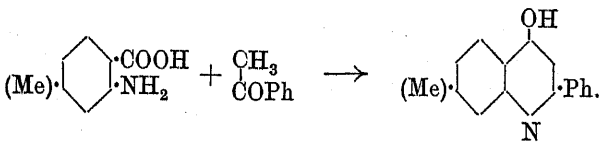


[1] *J. C. S.*, Abstr. 1894, i. 259; *Ber.*, 1894, **27**, 1394.
[2] v. Niementowski and Orzechowski, *ibid.*, 1895, **28**, 2809.
[3] D.R.-P. 347375/1920.

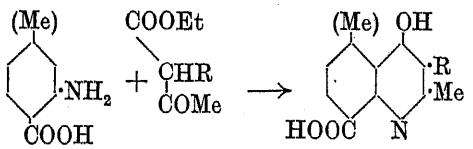
When furfural-anthranilic acid is treated with acetic anhydride the furan ring is opened and a complex compound is formed containing both a quinoline and a benzoxazine ring : [1]



The only simple *ketone* * with which v. Niementowski's method has been tried is acetophenone. When this is heated at 120–130° for three days with anthranilic acid or with *o*-amino-*p*-toluic acid the corresponding 2-phenyl-4-hydroxyquinoline is formed : [2]

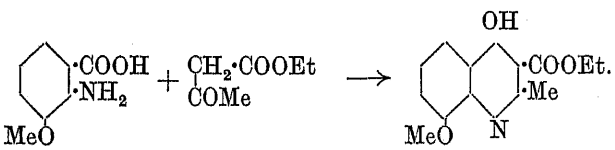


In the case of *acetoacetic ester* and its ethyl derivative a different type of reaction occurs : [3]



(R = H, Et.)

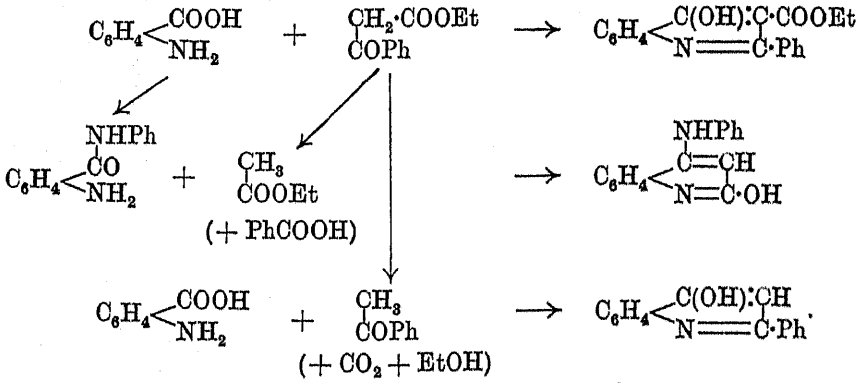
The normal reaction takes place when the vacant position *ortho* to the NH_2 is filled. For example, 3-methoxy-2-aminobenzoic acid yields 2-methyl-4-hydroxy-8-methoxyquinoline-3-carboxylic ester : [4]



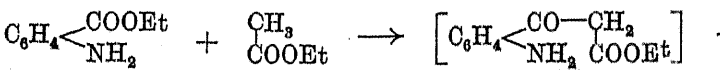
The reaction of anthranilic acid with benzoylacetic ester (50 hours at 140–150°) has been studied by v. Niementowski,[5] who isolated, in addition to the normal product, triphenylbenzene, benzoic

[1] Ekeley and Rogers, *J. A. C. S.*, 1922, **44**, 2655. [2] v. Niementowski, 1894, *loc. cit.*
[3] *Ibid.* [4] Froelicher and Cohen, *J. C. S.*, 1921, **119**, 1431.
[5] *Anz. Akad. Wiss. Krakov*, 1905, 285; 1907, 896; *Ber.*, 1905, **38**, 2044; 1907, **40**, 4285.
* For 2 : 5-naphthyridines from anthranilic acid and glutazine or trihydroxypyridine, see v. Niementowski and Sucharda, *J. pr. Chem.*, 1916, **94**, 193.

ester, aniline, 2-phenyl-4-hydroxyquinoline and 4-phenylaminocarbostyril. The three quinoline products seem to be produced by the following reactions :

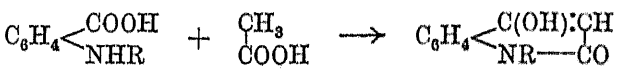


Anthranilic acid derivatives may also be converted into quinolines by condensation with esters of aliphatic *acids*. Erdmann [1] obtained 2 : 4-dihydroxyquinoline from anthranilic ester and acetic ester in the presence of sodium :



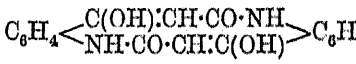
Alternatively, acetylanthranilic ester may be treated with sodium in toluene.[2] According to D.R.-P. 117167 ring-closure may be effected by heating potassium acetylanthranilate with solid KOH at 250° for an hour; this method gives satisfactory results.

N-Substituted anthranilic acids are converted into quinolines by heating with acetic anhydride : [3]

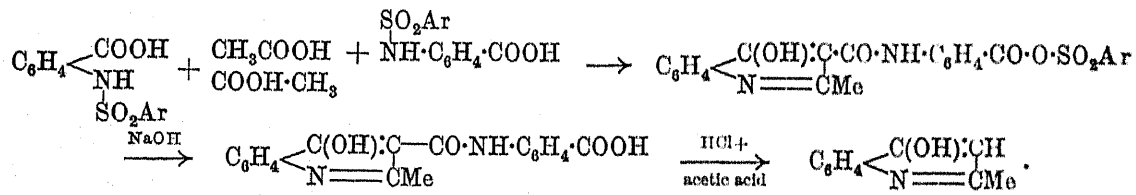


(R = Me, Ph, *o*-ClC_6H_4.)

An interesting condensation between anthranilic acid and two molecular proportions of acetic acid (*i.e.* equivalent to acetoacetic acid) has recently been elucidated by Heller and Grundmann.[4] By the action of $POCl_3$ upon acetanthranil, acetylanthranilic acid or its ester Anschütz and Schmidt obtained a compound which they considered to be



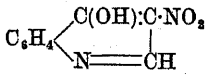
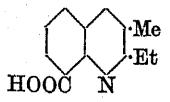
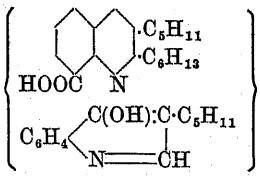
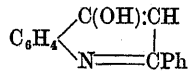
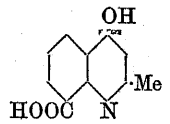
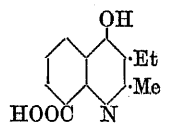
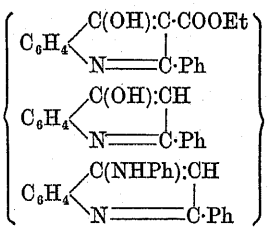
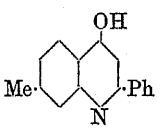
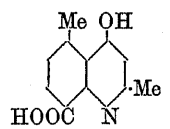
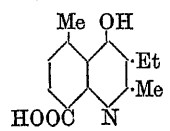
Heller and Grundmann have now prepared the same substance by successive treatment of benzene- or toluene-sulphonylanthranilic acid with acetic anhydride and NaOH, and have obtained from it, by hydrolysis with HCl in acetic acid at 140°, 4-hydroxyquinaldine :

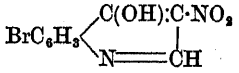
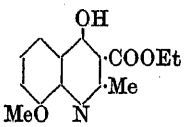
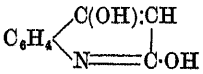
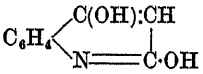
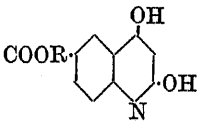
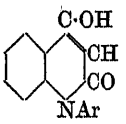
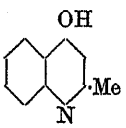


(*Anschütz and Schmidt's compound.*)

[1] *Ber.*, 1899, **32**, 3570.
[2] D.R.-P. 102894; see, however, Mühlstein, *Diss. Basle*, 1899.
[3] D.R.-P. 287803/1914.
[4] *Ber.*, 1923, **56**, 200.

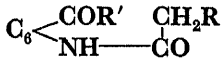
The following condensations have been described :

o-Amino-acid.	*Ketone etc.*	*Product.*	*References.*
Anthranilic acid.	Methazonic acid.		10
	Propionaldehyde.		2
	Œnanthaldehyde.		2
	Furfural.	(See p. 293.)	12
	Acetophenone.		1
	Acetoacetic ester.		1
	Ethylacetoacetic ester.		1
	Benzoylacetic ester.		7, 8
4-Methylanthranilic acid.	Acetophenone.		1
	Acetoacetic ester.		1
	Ethylacetoacetic ester.		1

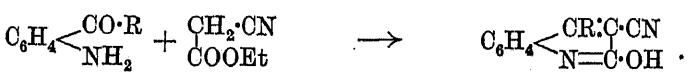
o-Amino-acid.	*Ketone etc.*	*Product.*	*References.*
5-Bromoanthranilic acid.	Methazonic acid.		10
3-Methoxyanthranilic acid.	Acetoacetic ester.		11
Anthranilic ester.	Acetic ester.		6
Acetylanthranilic ester.	Acetic ester.		4, 5
3-Acetylamino*iso*phthalic ester.	Acetic ester.		4
N-Methylanthranilic acid.	Acetic acid.		9
N-Phenylanthranilic acid.	Acetic acid.		
N-*o*-Chlorophenylanthranilic acid.	Acetic acid.		
Acetylanthranilic acid.	($POCl_3$)		13
N-Benzenesulphonylanthranilic acid.	Acetic acid.		
N-p-Toluenesulphonylanthranilic acid.	Acetic acid.		

References.

[1] v. Niementowski, *J. C. S.*, Abstr., 1894, i, 259; *Ber.*, 1894, **27**, 1394. [2] v. Niementowski and Orzechowski, *ibid.*, 1895, **28**, 2809. [3] v. Niementowski, *ibid.*, 1898, **28**, 2809. [4] D.R.-P. 102894. [5] Mühlstein, *Dissn. Basle*, 1899. [6] Erdmann, *Ber.*, 1899, **32**, 3570. [7] v. Niementowski, *Anz. Akad. Wiss. Krakov*, 1907, 285; *Ber.*, 1905, **38**, 2044. [8] *Idem*, *Anz. Akad. Wiss. Krakov*, 1907, 896; *Ber.*, 1907, **40**, 4285. [9] D.R.-P. 287803/1914. [10] D.R.-P. 347375/1920. [11] Froelicher and Cohen, *J. C. S.*, 1921, **119**, 1431. [12] Ekeley and Rogers, *J. A. C. S.*, 1922, **44**, 2655. [13] Anschütz and Schmidt, *Ber.*, 1902, **35**, 3473; Heller and Grundmann, *ibid.*, 1923, **56**, 200.

23. From acylated *o*-aminoaryl ketones etc.: 

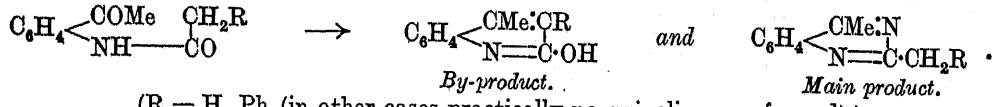
The first example of this type of quinoline synthesis was the preparation of 3-cyano-4-phenylcarbostyril by Guareschi: [1]



(R = Me, Ph.)

[1] *Ber.*, 1893, Ref. 944; *Zentr.*, 1894, ii, 211; *J. C. S.*, Abstr. 1895, i, 393.

About the same time Bischler and Howell,[1] by the action of alcoholic NH_3 upon acyl-*o*-aminoacetophenones, obtained, in addition to quinazolines, carbostyril derivatives as by-products:



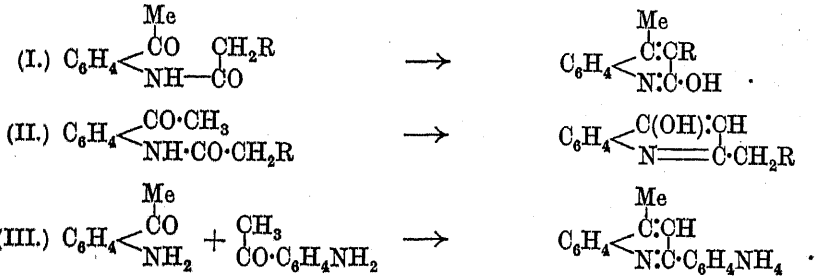
By-product. *Main product.*

(R = H, Ph (in other cases practically no quinoline was formed).)

Similarly, from phenylacetyl-*o*-aminobenzaldehyde and alcoholic KOH Bischler and Lang[2] prepared 3-phenylcarbostyril.

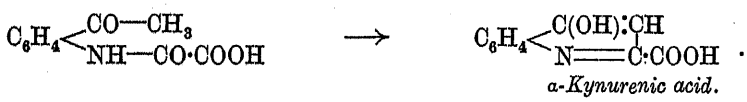
The method was developed in 1899 by Camps,[3] who applied it to a large number of acyl derivatives. Aqueous alcoholic NaOH was found to bring about the reaction.

The condensation may take three courses—either of the two CO groups may react, giving *α*- and *γ*-hydroxyquinolines respectively, and a third possibility is the removal of the acyl group and condensation to an *ortho*-flavaniline:



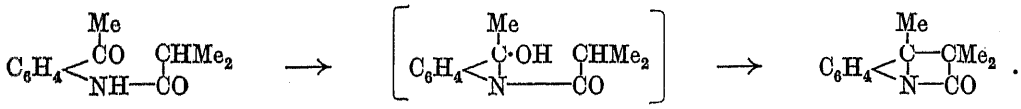
Usually a mixture of all three products is obtained, I and II being formed in largest quantity. As R becomes more negative the ·CH· group becomes more reactive and reaction I predominates: thus phenylacetylaminoacetophenone yields only one product, 3-phenyl-4-methylcarbostyril. Other negative groups (CN, ·COOEt, ·COMe, ·COPh) produce a similar result.[4]

Only reaction II is possible, of course, with formyl- and oxalyl-aminoacetophenones:

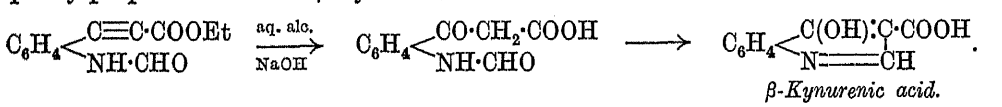


α-Kynurenic acid.

*iso*Butyryl-*o*-aminoacetophenone gives in addition to 2-*iso*propyl-4-hydroxyquinoline an appreciable amount of 3 : 3 : 4-trimethyl-2-keto-2 : 3-dihydroquinoline:



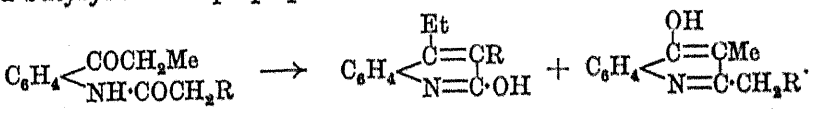
Formyl-*o*-aminobenzoylacetic acid is probably an intermediate in the conversion of formyl-*o*-aminophenylpropiolic ester into *β*-kynurenic acid:[5]



β-Kynurenic acid.

[1] *Ber.*, 1893, **26**, 1384–1399.
[2] *Ibid.*, 1895, **28**, 292.
[3] *Ibid.*, 1899, **32**, 3228; *Arch. Pharm.*, 1899, **237**, 659; 1901, **239**, 591.
[4] Camps, *Arch. Pharm.*, 1902, **240**, 135.
[5] *Idem, Zeitschr. physiol. Chem.*, 1901, **33**, 390.

Wöhnlich [1] determined the yields of α- and γ-hydroxyquinolines obtainable from acetyl-, propionyl- and butyryl-*o*-aminopropiophenones :



Acyl group :	*R.*	%α-OH(I).	%γ-OH(II).
Acetyl.	H	85	12
Propionyl.	Me	54	40
Butyryl.	Et	33	53

The following condensations have been described :

(a) o-*Aminobenzaldehyde :*

Acyl group (or keto-ester etc.).	*Substituents in resulting quinolines.* 2	3	4	*References.*
Acetyl.	OH	H	H	5
Phenylacetyl.	OH	Ph	H	4
Succinyl.	OH	$\cdot CH_2COOH$	H	12
Cyanacetic ester.	OH	CN	H	1

(b) o-*Aminoacetophenone :*

Formyl.	H	H	OH	7
Acetyl.	OH	H	Me	2, 5
	Me	H	OH	
Phenylacetyl.	OH	Ph	Me	2, 8
*iso*Butyryl.	$CHMe_2$	H	OH	8
Benzoyl.	Ph	H	OH	8
Carbethoxy.	OH	H	OH	8
Oxalyl.	$\cdot COOEt$	H	OH	7, 13
Malonic ester.	OH	$\cdot COOEt$	Me	10
Cyanacetic ester.	OH	CN	Me	1, 10
Acetoacetic ester.	OH	$\cdot COMe$	Me	10
Benzoylacetic ester.	OH	$\cdot COPh$	Me	10

(c) o-*Aminopropiophenone :*

Acetyl.	OH	H	Et	11
	Me	Me	OH	
Propionyl.	OH	Me	Et	11
	Et	Me	OH	
Butyryl.	C_2H_7	Me	OH	11
	OH	Et	Et	
Benzoyl.	Ph	Me	OH	11

(d) o-*Aminobenzophenone :*

Acetyl.	OH	H	H	5, 6
Cyanacetic ester.	OH	CN	Ph	3

(e) o-*Aminobenzoic acid (anthranilic acid) :*

Acetyl.	OH	H	OH	5

(f) o-*Aminobenzoylformic acid (isatic acid) :*

Acetyl.	OH	H	COOH	5
Phenylacetyl.	OH	Ph	COOH	6

[1] *Arch. Pharm.*, 1913, **251**, 526.

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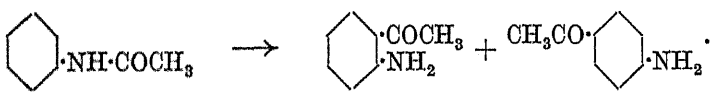
Acyl group (or keto-ester etc.).	*Substituents in resulting quinolines.* 2	3	4	*References.*
(g) *o-Aminobenzoylacetic ester :*				
Acetyl.	OH	H	$\cdot CH_2COOH$	5
(h) *o-Aminophenyl benzyl ketone :*				
Acetyl,	OH	H	CH_2Ph	5
	Me	Ph	OH	
(k) *o-Aminobenzoylmethyl :*				
Acetyl,	OH	H	CH_2OH	5

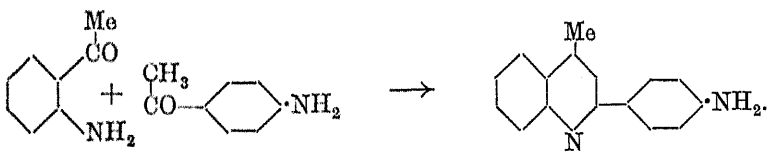
References.

[1] Guareschi, *Ber.*, 1893, Ref. 944. [2] Bischler and Howell, *ibid.*, 1893, **26**, 1397. [3] Guareschi, *J. C. S.*, Abstr., 1895, i, 393; *Zentr.*, 1894, ii, 211. [4] Bischler and Lang, *Ber.*, 1895, **28**, 292. [5] Camps, *ibid.*, 1899, **32**, 3228. [6] *Idem, Arch. Pharm.*, 1899, **237**, 659. [7] *Idem, Zeitschr. physiol. Chem.*, 1901, **33**, 390. [8] *Idem, Arch. Pharm.*, 1901, **239**, 591. [9] *Idem, Ber.*, 1901, **34**, 2709–2716. [10] *Idem, Arch. Pharm.*, 1902, **240**, 135. [11] Wöhnlich, *ibid.*, 1913, **251**, 526. [12] Perkin and Robinson, *J. C. S.*, 1913, **103**, 1975. [13] Späth, *Sitzber. Akad. Wiss. Wien*, 1921, **130**, iib, 93; *Monatsh.*, 1921, **42**, 89.

24. The flavaniline synthesis : $C_6{<}^{COMe}_{NH_2} + {}^{CH_3}_{CO\cdot Ar}$

Flavaniline is a dyestuff, now obsolete, formerly manufactured from acetanilide by heating with $ZnCl_2$ [1] or with excess acetic anhydride.[2] Diphenylacetamidine and $ZnCl_2$ give the same product.[3] The constitution of the product and the mechanism of its synthesis were elucidated by Besthorn and Fischer.[4] The acetyl group migrates from the nitrogen to *o*- and *p*-positions, and the products so formed condense to a quinoline as in Friedländer's method :

(i) 

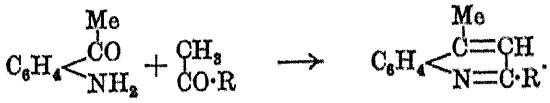
(ii) 

Flavaniline.

O. Fischer [5] showed that reaction (ii) could be repeated with a mixture of *o*- and *p*-aminoaceto-

[1] D.R.-P. 19766/1881; O. Fischer and Rudolph, *Ber.*, 1882, **15**, 1500. [2] D.R.-P. 27948/1883.
[3] D.R.-P. 28323/1882. [4] *Ber.*, 1883, **16**, 68. [5] *Ibid.*, 1886, **19**, 1036.

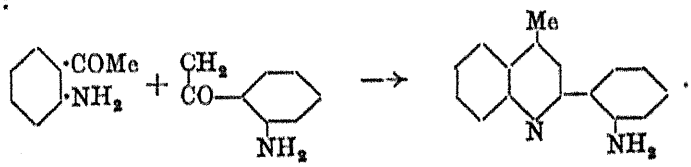
phenones in the presence of NaOH, and that quinolines were also formed when the *p*-aminoacetophenone was replaced by paraldehyde, acetone or acetophenone :



(R = H, Me, Ph, *p*-$NH_2C_6H_4$.)

The product from acetophenone contains the Flavaniline skeleton and was called Flavoline.

o-Flavaniline was synthesised by Bischler and Burkart [1] from *o*-aminoacetophenone by boiling it with formic acid :

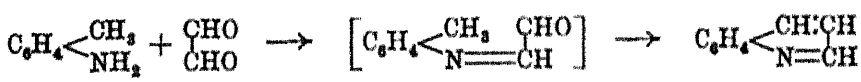


o-Flavaniline and its acyl derivatives are formed in small amount in the synthesis of quinolines by Camps' method (see preceding section).

Goldschmidt [2] heated acetophenone oxime with P_2O_5 at 60°. The acetanilide first formed (by Beckmann transformation) is converted under these conditions into Flavaniline.

26. From *o*-toluidine: $C_6\langle^{CH_2-}_{N=C}\rangle^{CO-}$

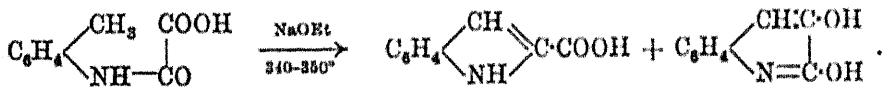
Quinoline was prepared in 35–40% yield by Kulisch [3] from *o*-toluidine and glyoxal heated to 150° with NaOH :



The reaction fails with benzil.[4] *o*-Toluidine and pyruvic ester gave, in the presence of alcoholic $ZnCl_2$, a compound $C_{10}H_9ON$: [5]



A similar reaction accounts for the formation of a small amount (20% of the total condensation product) of 2 : 3-dihydroxyquinoline in Madelung's indoxylic acid synthesis : [6]

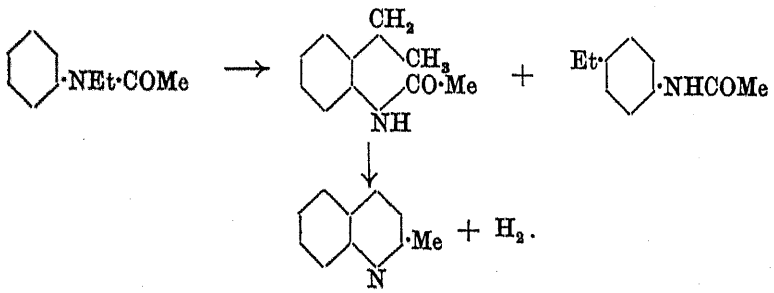


(10 gms.) (1·7 gms.) (0·4 gm.)

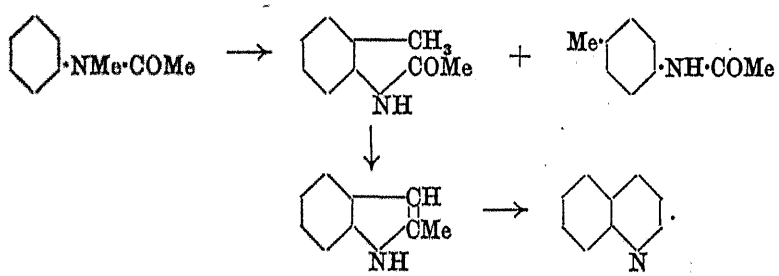
[1] *Ber.*, 1893, **26**, 1352. [2] *Chem. Zeitung*, 1903, **27**, 279. [3] *Monatsh.*, 1894, **15**, 276.
[4] Kulisch, *ibid.*, 1895, **16**, 351. [5] *Idem*, *ibid.*, p. 355. [6] *Ber.*, 1912, **45**, 3521.

26. From *o*-acylamino compounds—ring closure in α:β-position: $C_6<\begin{matrix}C—CH_2\cdot R'\\N—CO\cdot R\end{matrix}$

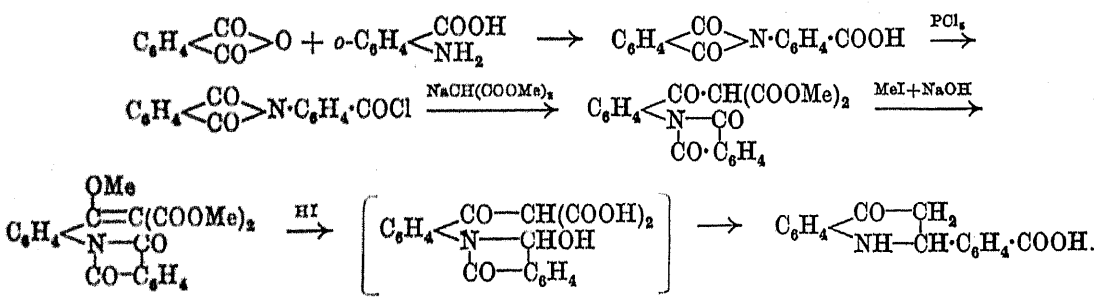
Bunzl [1] heated acetylethylaniline with $ZnCl_2$ and obtained, in place of the expected ethylated flavaniline, quinaldine. The ethyl group migrates in preference to the acetyl group:



Acetylmethylaniline under similar conditions [2] gives quinoline—probably *via* 2-methylindole:



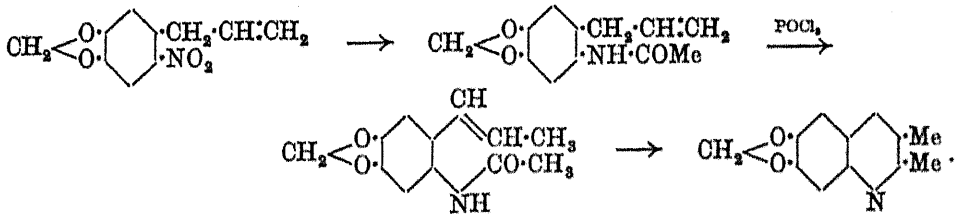
An interesting quinoline synthesis by α:β-ring closure is that of Gabriel and Ladenburg: [3]



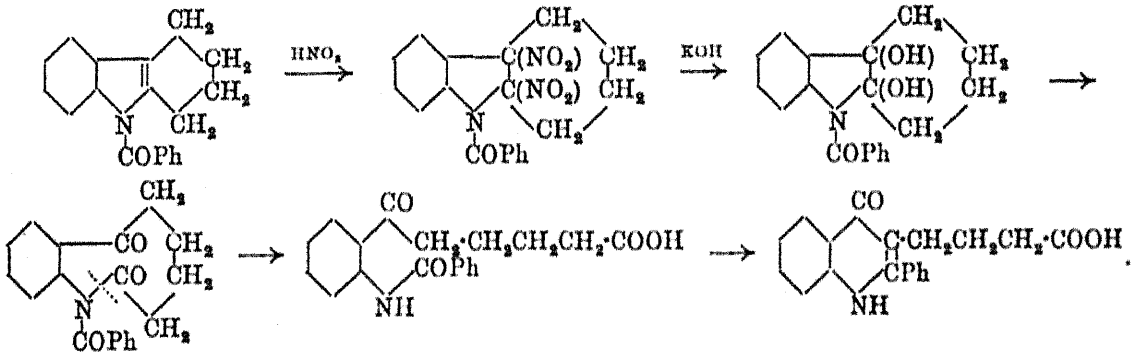
The number of reactions brought about by the HI in the final stage is remarkable. The methoxy group is hydrolysed, the two ester groups are eliminated, one of the phthalyl ·CO· groups is reduced to ·CH(OH)·, the phthalimide grouping is semi-hydrolysed and the quinoline ring is closed.

[1] *Ber.*, 1889, **22**, 1847. [2] Pictet and Fert, *ibid.*, 1890, **23**, 1903. [3] *Ibid.*, 1918, **51**, 1493.

Foulds and Robinson [1] prepared a methylenedioxy-dimethylquinoline from *o*-nitrosafrole:



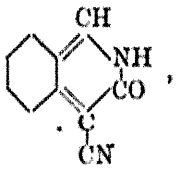
The curious conversion of *N*-benzoyltetrahydrocarbazole into a quinoline derivative by the successive action of nitric acid and boiling KOH [2] belongs to this group:



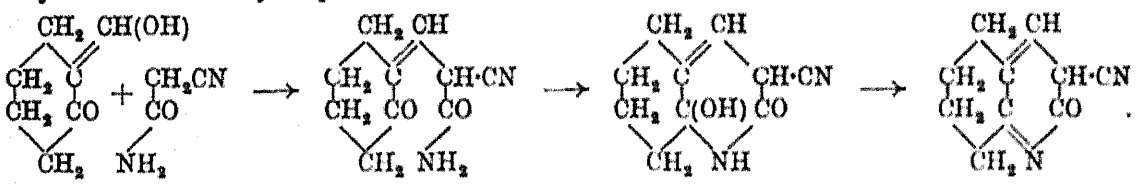
N-Acetyltetrahydrocarbazole behaves differently (see Indoles, p. 145).

27. Sen-Gupta's synthesis from cyanacetamide: $C_6\langle^{C}_{OH}{-}{-}{-}^{C}_{NH_2}\rangle C$

Sen-Gupta,[3] in the hope of obtaining



condensed hydroxymethylene*cyclo*hexanone with cyanacetamide. The product proved to be 3-cyano-2-keto-hexahydroquinoline:



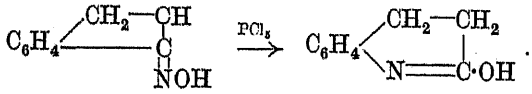
(By-product.)

Similar products are obtained from hydroxymethylene derivatives of 2-, 3- and 4-methyl-*cyclo*hexanones and of menthone.

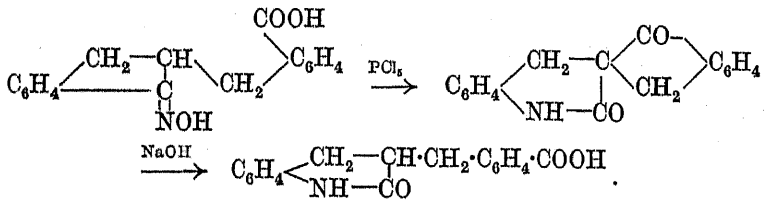
[1] *J. C. S.*, 1914, 105, 1968.
[2] Perkin and Plant, *ibid.*, 1923, 123, 676.
[3] *Ibid.*, 1915, 107, 1347—1367.

28. From hydrindone oxime:

The oximes of cyclic ketones, as Wallach has shown, undergo the Beckmann isomerisation when heated with PCl, etc. Thus the oxime of *cyclo*pentanone gives piperidone (p. 235). This reaction has been applied by Kipping [1] to hydrindone oxime, the product being dihydrocarbostyril:

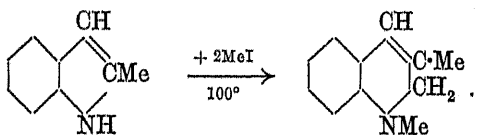


A similar reaction was described by Leuchs and Ranch: [2]

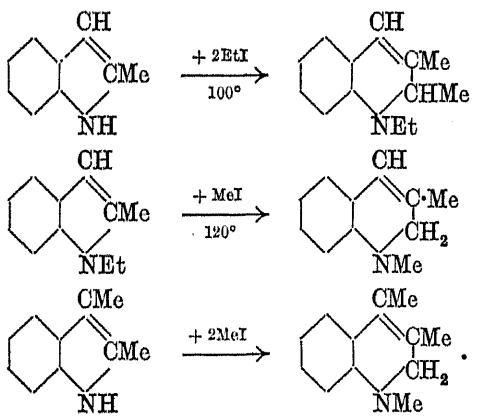


29. From indoles:

Fischer and Steche [3] found that when two molecular proportions of methyl iodide are heated with 2-methylindole at 100°, not only is the ·NH· group methylated, but the ring is enlarged and a dihydroquinoline results. This product is formed to the extent of 80% of the weight of methylindole used:

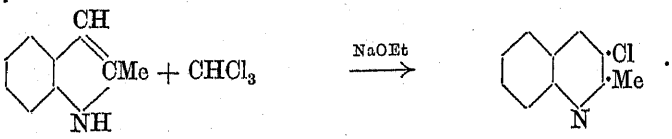


The reaction appears to be quite general. Thus:

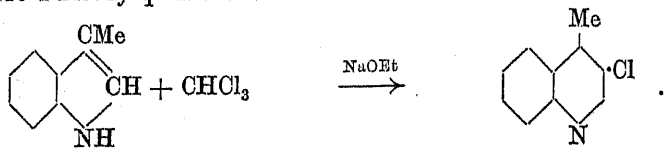


[1] *J. C. S.*, 1894, **65**, 489. [2] *Ber.*, 1915, **48**, 1536. [3] *Ann.*, 1887, **242**, 353, 360, 363, 364.

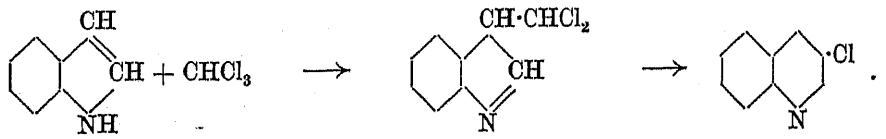
Magnanini [1] observed a similar widening of the indole ring when 2-methylindole is treated with $CHCl_3$ and NaOEt:



Scatole (3-methylindole) in the same way gives a product which Ellinger and Flamand [2] showed to be 3-chloro-4-methylquinoline:

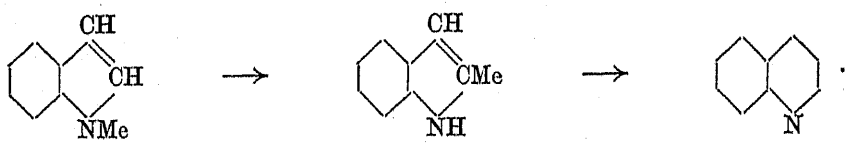


Ellinger [3] obtained 3-chloroquinoline from the non-methylated indole. He considers that dichloromethylindolenine is an intermediate product:



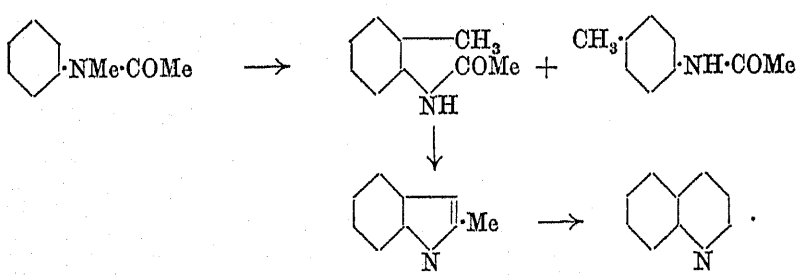
The reaction was applied to 6-methoxyindole by Kermack, Perkin and Robinson.[4]

Alkylated indoles may also be transformed into quinolines by passing through a tube heated to dull redness. Thus *N*-methyl- or 2-methyl-indole gives a 17% yield of quinoline: [5]



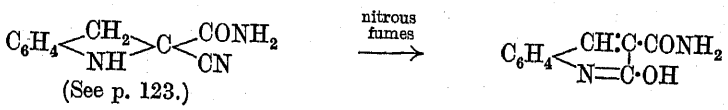
(Cf. pyridine from 2-methylpyrrole, p. 239.)

This explains Fischer and Steche's observation [6] that quinolines are formed in the Fischer indole synthesis when the temperature is allowed to rise too high. The formation of quinoline from acetylmethylaniline [7] is similarly accounted for:



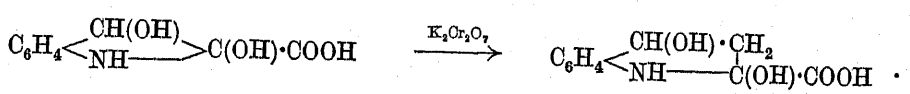
[1] *Ber.*, 1887, **20**, 2608; 1888, **21**, 1940. [2] *Ibid.*, 1906, **39**, 4388. [3] *Ibid.*, p. 2521.
[4] *J. C. S.*, 1922, **121**, 1882. [5] Pictet, *Ber.*, 1905, **38**, 1946. [6] *Ibid.*, 1887, 20, 819.
[7] Pictet and Fert, *ibid.*, 1890, **23**, 1903.

Certain indolecarboxylic acids have been converted into carbostyril derivatives by Heller and Wunderlich : [1]



(See p. 123.)

and by Heller : [2]



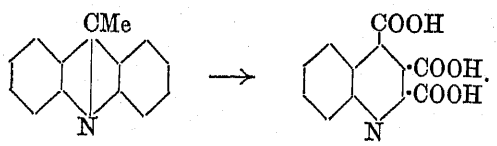
Isatin is converted by diazomethane into 2 : 3-dihydroxyquinoline : [3]



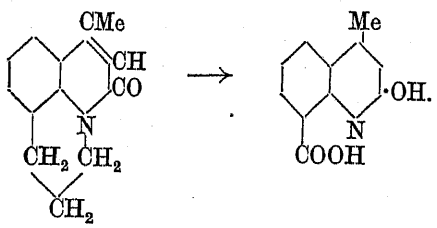
The lactam form of 5 : 7-dimethylisatin behaves in the same way, but the lactim form gives an isomeride.

30. By oxidation of acridines etc :

The oxidation of acridines by $KMnO_4$ gives quinoline-2 : 3-dicarboxylic acids, just as quinoline is converted into quinolinic acid. Thus Bernthsen [4] oxidised 5-methylacridine to quinoline-2 : 3 : 4-tricarboxylic acid :



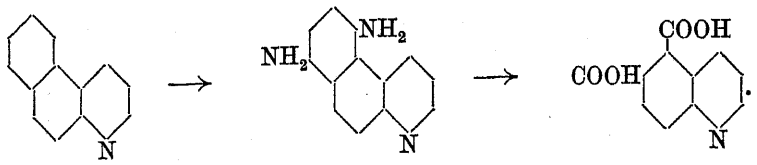
Similarly, the oxidation of methylketojuloline [5] gives 4-methylcarbostyril-8-carboxylic acid :



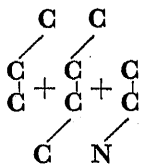
The naphthoquinoline obtained by Skraup's reaction from β-naphthylamine can be converted

[1] *Ber.*, 1914, **47**, 1617–1629. [2] *Ibid.*, 1918, **51**, 434. [3] Heller, *ibid.*, 1919, **52**, 741.
[4] *Ann.*, 1884, **224**, 1. [5] Reissert, *Ber.*, 1891, **24**, 841.

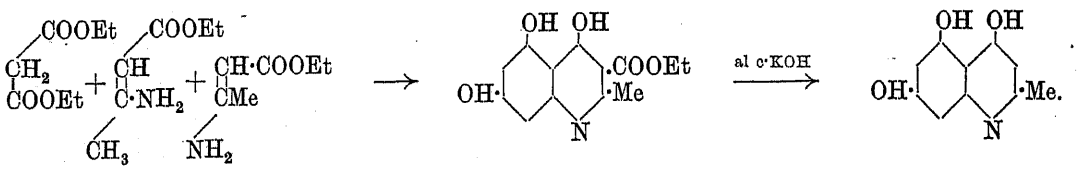
into quinoline-5 : 6-dicarboxylic acid by dinitration and reduction followed by oxidation of the diamine : [1]



31. From β-aminocrotonic ester and malonic ester :



Knoevenagel and Fries [2] condensed malonic ester with two molecular proportions of β-amino-crotonic ester :

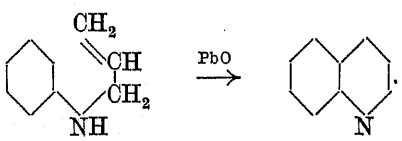


The carbethoxy-group of the condensation product may be in position 3 or 6.

The reaction does not appear to have been applied to substituted malonic esters or to other unsaturated amines.

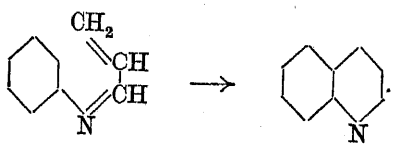
32. Pyrogenous methods :

The first synthesis of quinoline was achieved by Koenigs, who passed allylaniline over heated litharge : [3]

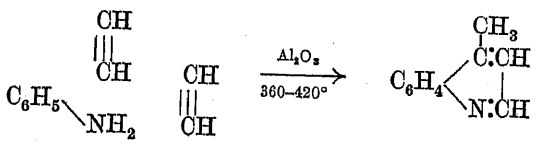


[1] Hepner, *Monatsh.*, 1907, **27**, 1045. [2] *Ber.*, 1898, **31**, 773; 1902, **35**, 2178. [3] *Ibid.*, 1880, **13**, 453.

A little later [1] Koenigs also obtained quinoline in 7% yield by dry distillation of acrolein-aniline (*cf.* Skraup reaction, p. 245):



Just as C_2H_2 alone gives benzene when passed through a hot tube, and a mixture of C_2H_2 and NH_3 gives pyridine, so from C_2H_2 and aniline a small amount of lepidine results: [2]

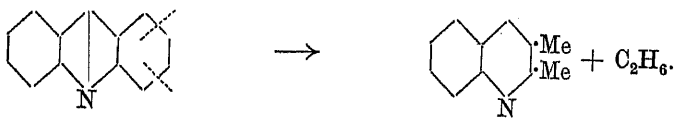


Meyer and Wesche [3] have investigated very thoroughly the pyrogenous condensations of acetylene. They find that from 1250 litres of acetylene and 250 litres of ammonia passed through a hot tube 380 grams of tar are obtained containing 58 grams of crude quinoline, b. p. 200–250°. This is equivalent to a yield of rather less than 4%:

$$5C_2H_2 + NH_3 \longrightarrow C_9H_7N + CH_4 + H_2.$$

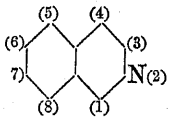
Majima, Unno, and Ono [4] obtained only traces of quinoline from a mixture of 1 kilogram of aniline, 53 litres of C_2H_2 and 21 litres of CO_2 passed through an iron tube at 700°.

Acridine when passed with hydrogen over reduced nickel at 250–270° gives, not the expected methylated carbazole (cf. quinoline ⟶ 2-methylindole, p. 145), but 2 : 3-dimethylquinoline: [5]



[1] *Ber.*, 1880, **1,3** 911.
[2] Tschitschibabin, *J. Russ.*, 1916, **47**, 703; *Zentr.*, 1916, i, 921.
[3] *Ber.*, 1917, **50**, 424, 434.
[4] *Ibid.*, 1922, **55**, 3854.
[5] Padoa and Fabris, *R. A. L.*, 1907, [v], **16**, i, 921.

CHAPTER IX

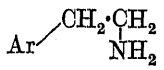
*iso*QUINOLINES, 

Introductory:

THE *iso*quinoline syntheses include examples of ring-closure in all the five possible positions in the Py-ring—nucleus-1, 1-2, 2-3, 3-4 and 4-nucleus. They may be grouped as follows:

I. *Ring-closure between nucleus and carbon atom* (1):

The technically important methods (sects. 1 and 2) start from β-arylphenylethylamines



which may be condensed with acids (sect. 1) or with aldehydes (sect. 2), the ring being then closed by means of P_2O_5 or HCl. The products in the first case are *dihydro*iso*quinolines*, in the second *tetrahydro* derivatives. A modification of the second method uses chloromethyl ether in place of aldehydes (sect. 3). These methods have been very useful in the synthesis of a number of *iso*quinoline alkaloids, especially of hydrastinine.

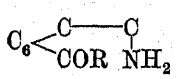
The Beckmann change (sect. 4) applied to oximes of the type



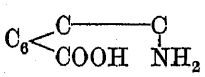
gives only poor yields of iso*quinolines*, though rather better results are obtained with the corresponding saturated oximes. No dihydro*iso*carbostyril is formed from hydrindone oxime (see p. 303).

II. *Ring-closure between nitrogen and carbon atom* (1) *or* (3):

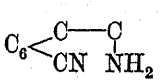
β-Arylethylamines carrying a suitable *ortho* carbon group may serve as a source of *iso*quinoline derivatives (sects. 5–8). This may be a ketonic group (sect. 5), a carboxyl group (sect. 6), a nitrile group (sect. 7) or an aminomethyl group (sect. 8).



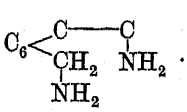
(I.)



(II.)



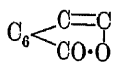
(III.)



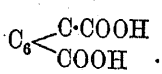
(IV.)

No simple example of the first type (I) has been described. The second type (II) gives iso*carbostyrils* or *dihydro*iso*carbostyrils*. Addition at the ·CN group (III) leads to imino compounds which are readily hydrolysed to iso*carbostyrils*, while the usual elimination of NH_3 from a diamine (IV) has recently been applied to the preparation of *tetrahydro*iso*quinoline*.

*iso*Coumarins (VI) and homophthalic acids (VII) are readily converted into iso*carbostyrils* (sect. 9) and *homophthalimides* (sect. 10) respectively by the action of ammonia or primary amines:



(VI.)



(VII.)

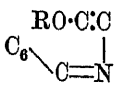
o-Cyanobenzyl cyanide may be used for the preparation of *hŏmophthalimide* (sect. 7) or of various 4-*cyano*-iso*carbostyrils* (sect. 11) carrying substituents in position 3.

III. *Ring-closure between carbon atoms* (3) *and* (4):

Phthalyl derivatives of *a*-amino-esters give 2 : 4-*dihydroxy*iso*quinolines* when treated with NaOEt (sect. 12) and a similar condensation occurs with α-phthaliminoketones (sect. 12).

IV. *Ring-closure between carbon atom* (4) *and nucleus:*

The elimination of water (or alcohol) from compounds of the type

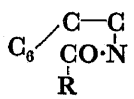


(R = H or alkyl.)

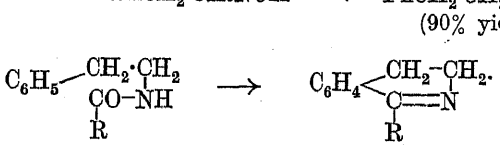
gives iso*quinolines* (sect. 13). These substances are prepared from aminoacetal and aldehydes, or from chloroacetal and benzylamines. Benzoylaminoacetal gives iso*carbostyril* (sect. 13).

The conversion of hippuric acid into *dichloro*iso*quinoline* (sect. 14) is not a general synthetic method.

V. *Pyrogenous methods.* (See section 15.)

1. From acylated β-phenylethylamines: 

Bischler and Napieralski [1] obtained small yields of methyl- and phenyl-dihydro*iso*quinolines by heating acetyl- and benzoyl-β-phenylethylamines with P_2O_5 or $ZnCl_2$ at 200°:



(90% yield.)

(R = Me, Ph.)

[1] *Ber.*, 1893, **26**, 1903.

The method was generalised many years later by Pictet,[1] who found that Bischler's conditions were too drastic, much better results being obtained by heating with P_2O_5 in boiling toluene or xylene for 15 minutes. The yields were thus increased to about 75% in the case of methyl-, phenyl- and benzyl-dihydro*iso*quinolines.

Decker [2] independently improved the Bischler-Napieralski synthesis by the use of toluene or xylene as a solvent with various condensing agents—$AlCl_3$, PCl_5, $POCl_3$, P_2O_5, $FeCl_3$ or $ZnCl_2$.

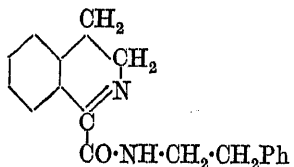
In the case of formyl-phenylethylamine the main product is an aminomalonamide (I),

$$PhCH_2{\cdot}CH_2{\cdot}NH{\cdot}CH\begin{matrix}<\text{CO}{\cdot}\text{NH}{\cdot}\text{CH}_2{\cdot}\text{CH}_2\text{Ph}\\ \text{CO}{\cdot}\text{NH}{\cdot}\text{CH}_2{\cdot}\text{CH}_2\text{Ph}\end{matrix}$$

(I.)

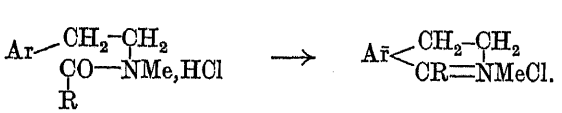
the constitution of which was elucidated by Decker and Becker.[3] A small amount of dihydro-*iso*quinoline is, however, isolable.[4]

Only one ring-closure occurs with the oxalyl compound, the product being (II) :

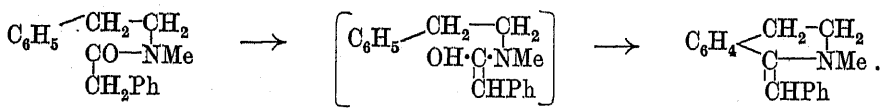


(II.)

*iso*Quinoline formation occurs even when the ·NH· group is alkylated : [5]



The phenylacetyl derivative of β-phenylethyl-methylamine is converted by P_2O_5 in xylene into 1-benzal-*N*-methyl-tetrahydro*iso*quinoline.[6]



The Bischler-Napieralski method, as modified by Pictet and Decker, has found considerable application in the synthesis of *iso*quinoline alkaloids—laudanosine, papaverine, cotarnine,

[1] Pictet and Kay, *Ber.*, 1909, **42**, 1973; Pictet and Finkelstein, *ibid.*, p. 1979; Pictet and Gams, *ibid.*, p. 2943.

[2] Decker and Kropp, *ibid.*, p. 2075; D.R.-PP. 234850, 235358, 245095, 267699, 279194; Decker, Kropp, Hoyer and Becker, *Ann.*, 1913, **395**, 299–320.

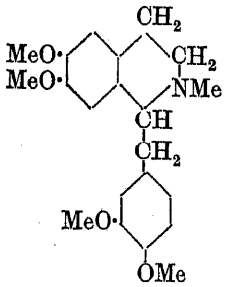
[3] *Ibid.*, 1911, **382**, 369.

[4] Decker, Kropp, Hoyer and Becker, *loc. cit.*

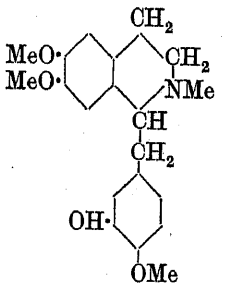
[5] D.R.-PP. 267699, 279194.

[6] Hamilton and Robinson, *J. C. S.*, 1916, **109**, 1029.

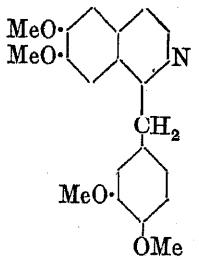
hydrastinine, laudanine, anhalonidine, pellotine and anhalonine have all been synthesised in this way.



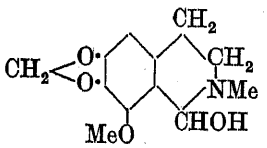
Laudanosine.
(Pictet and Finkelstein, 1909.)



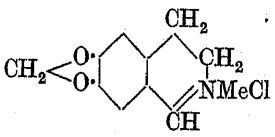
Laudanine.
(Späth and Lang, 1921.)



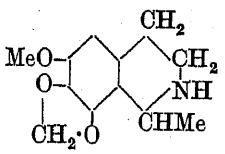
Papaverine.
(Pictet and Gams, 1909.)



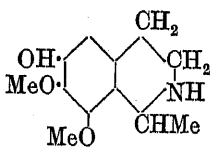
Cotarnine (cyclic form).
(Salway, 1910; Decker and Becker, 1913.)



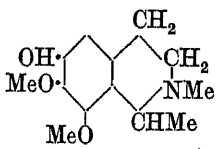
Hydrastinine chloride.
(Decker, 1911, 1913; Decker and Becker, 1913.)



Anhalonine.
(Späth and Gangl, 1923.)

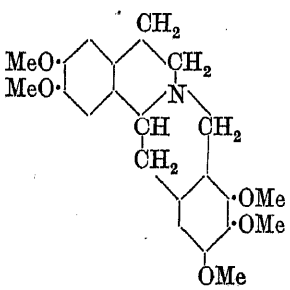


Anhalonidine.
(Späth, 1923.)

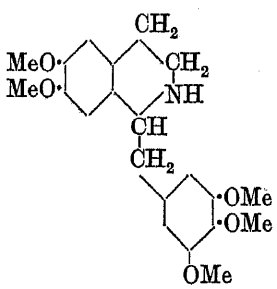


Pellotine.
(Späth, 1923.)

An attempt to obtain tetrahydrocolumbamine (III) from the *iso*quinoline (IV) by condensation with methylal was unsuccessful. The *iso*quinoline (IV) was prepared by the Pictet-Decker method : [1]



(III.)



(IV.)

[1] Späth and Böhm, *Ber.*, 1922, **55**, 2985.

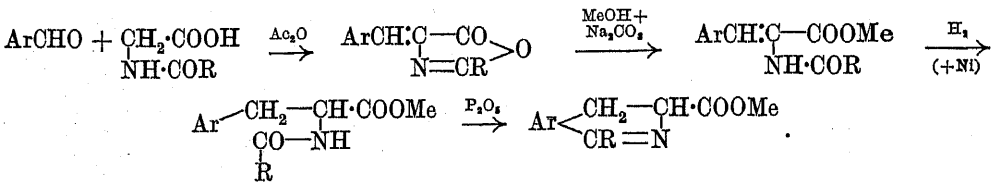
For the preparation of the β-arylethylamines required for these syntheses several methods have been devised, but all are somewhat laborious. Bischler and Napieralski reduced the oxime of phenylacetaldehyde (see p. 309). Pictet, Decker and others have condensed the appropriate aromatic aldehyde with nitromethane :

$$ArCHO + CH_3{\cdot}NO_2 \longrightarrow ArCH{:}CH{\cdot}NO_2 \xrightarrow{H_2} ArCH_2{\cdot}CH{:}NOH \xrightarrow{H_2} ArCH_2CH_2NH_2.$$

Decker and Salway have also employed the Hofmann reaction :

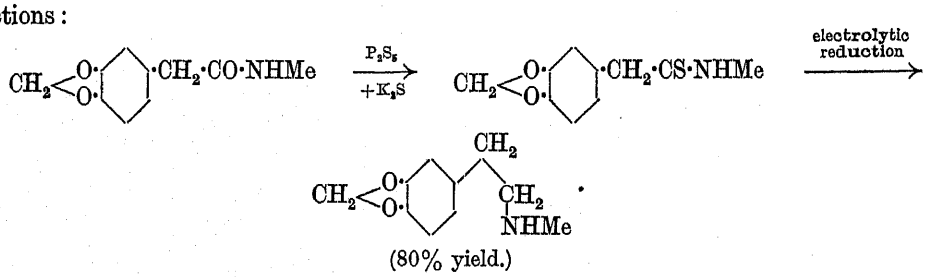
$$Ar{\cdot}CH_2{\cdot}CH_2{\cdot}CONH_2 \xrightarrow[NaOH]{NaOCl+} ArCH_2{\cdot}CH_2{\cdot}NH_2.$$

In a recently patented method [1] an acylated β-arylethylamine derivative is obtained from the condensation product of the aldehyde with acylated glycines :



The aldehydes used here are piperonal and veratraldehyde, the glycines being benzoyl-, cinnamoyl- and veratroyl-glycines.

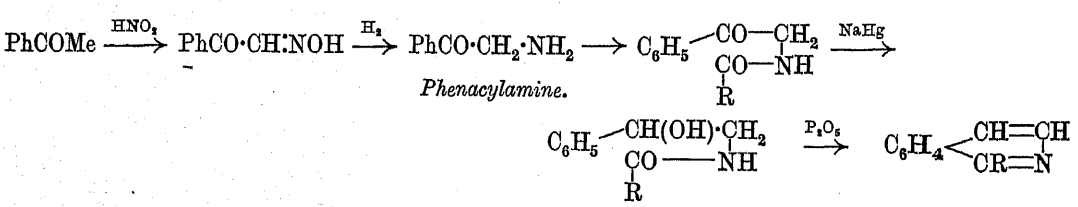
Kindler [2] has obtained *N*-methylpiperonylamine in very good yield by the following series of reactions :



(80% yield.)

The formyl derivative is converted into hydrastinine by the usual method.

Phenacylamines are much more easily accessible than the corresponding phenylethylamines. They may be reduced to the secondary alcohols and from these *iso*quinolines (instead of dihydro-*iso*quinolines) are obtained : [3]

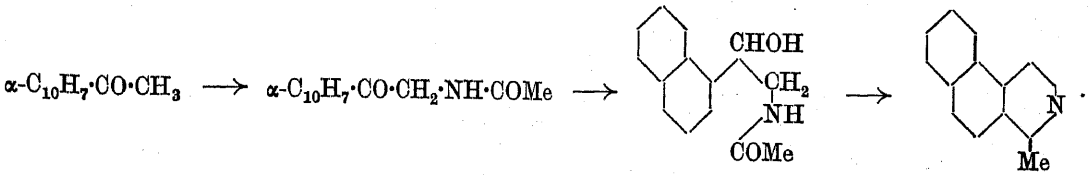


Phenacylamine.

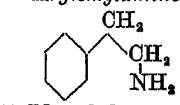
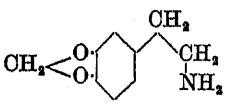
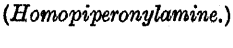
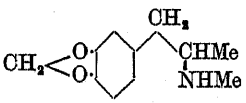
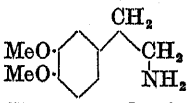
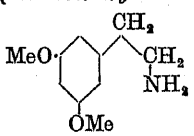
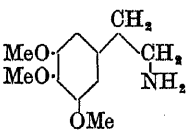
(R = H, Me, Ph, ·CH_2Ph.)

[1] E.P. 191233; A.P. 1437802; Swiss Pats. 92004, 92610, 92611, 92612.
[2] *Ann.*, 1923, **431**, 229.
[3] Pictet and Gams, *Ber.*, 1910, **43**, 2384.

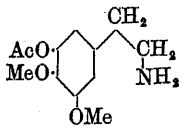
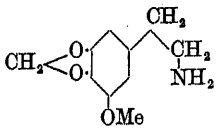
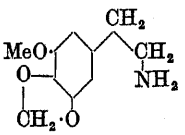
Papaverine, which cannot be obtained from dihydropapaverine (an intermediate stage in the synthesis of laudanosine), was synthesised by this means.[1] The method has also been employed by Pictet and Manevitch [2] for the preparation of a naphth*iso*quinoline :



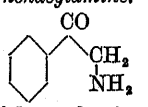
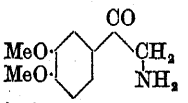
*Dihydro*iso*quinolines* have been synthesised by this method from the following amines and acids :

Arylethylamine.	*Acyl group.*	*References.*
 (*β-Phenylethylamine.*)	H·CO	4, 15
	Me·CO	1, 2
	$PhCH_2·CO$	2, 4, 15
	Ph·CO	1, 2, 4, 15
	COOH·CO	11, 15
N-Methyl derivative	H·CO	12, 13
	$PhCH_2·CO$	18
 (*Homopiperonylamine.*)	H·CO	9, 11, 15, 16
	Me·CO	10, 15
	$PhCH_2·CO$	10, 15
	Ph·CO	10, 15, 19
	$(MeO)_2C_6H_3·CH_2·CO$	19
		4, 15, 16
	Ph·CH:CH·CO	19
N-Methyl derivative.	H·CO	12, 25
	Ph·CO	12
N-Ethyl derivative.	H·CO	12
	H·CO	13
 (*Homoveratrylamine.*)	Ph·CO	19
	PhCH:CH·CO	19
	$(MeO)_2C_6H_3·CH_2·CO$	3, 19
	$(MeO)_3C_6H_2·CH_2·CO$	22
	$PhCH_2·CO$	8
	Me.CO	20

[1] Pictet and Gams, *Ber.*, 1909, **42**, 2943. [2] *Zentr.*, 1913, i, 1032.

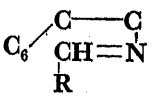
Arylethylamine.	*Acyl group.*	*References.*
	Me·CO	23
 (*Homomyristicylamine.*)	H·CO $PhCH_2$·CO	11, 16 7
	Me·CO	24

Pictet and Gams' method (from phenacylamines) has been used in the following cases, the products after acylation, reduction and condensation being iso*quinolines*:

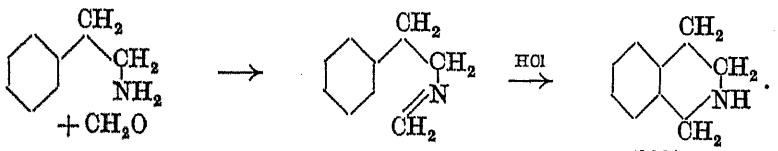
Phenacylamine.	*Acyl group.*	*References.*
 (*Phenacylamine.*)	H·CO Me·CO $PhCH_2$·CO Ph·CO	6
 (*Aminoacetoveratrone.*)	$(MeO)_2$·C_6H_3·CH_2·CO	5
α-$C_{10}H_7$·CO·CH_2·NH_2	Me·CO	17

References.

[1] Bischler and Napieralski, *Ber.*, 1893, **26**, 1903. [2] Pictet and Kay, *ibid.*, 1909, **42**, 1973. [3] Pictet and Finkelstein, *ibid.*, p. 1979. [4] Decker and Kropp, *ibid.*, p. 2075. [5] Pictet and Gams, *ibid.*, p. 2943. [6] *Idem*, *ibid.*, 1910, **43**, 2384. [7] Salway, *J. C. S.*, 1910, **97**, 1208. [8] *Idem*, *ibid.*, 1911, **99**, 1320. [9] D.R.-P. 234850. [10] D.R.-P. 235358. [11] D.R.-P. 245095. [12] D.R.-P. 267699. [13] D.R.-P. 279194. [14] Decker, *Zeitschr. angew. Chem.*, 1911, **24**, 1890. [15] Decker, Kropp, Hoyer and Becker, *Ann.*, 1913, **395**, 299–320. [16] Decker and Becker, *ibid.*, p. 329. [17] Pictet and Manevitch, *Zentr.*, 1913, i, 1032. [18] Hamilton and Robinson, *J. C. S.*, 1916, **109**, 1029. [19] E.P. 191233; A.P. 1437802; Swiss PP. 92004, 92610–92612. [20] Späth, *Monatsh.*, 1921, **42**, 97. [21] Späth and Lang, *ibid.*, p. 273. [22] Späth and Böhm, *Ber.*, 1922, **55**, 2985. [23] Späth, *Monatsh.*, 1922, **43**, 477. [24] Späth and Gangl, *ibid.*, 1923, **44**, 111. [25] Kindler, *Ann.*, 1923, **431**, 229.

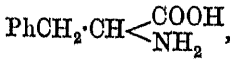
2. From β-arylethylamines and aldehydes: 

Just as acids and β-arylethylamines can be condensed to form dihydro*iso*quinolines, so aldehydes yield tetrahydro*iso*quinolines. The alkylidene- or arylidene-derivative is first produced, and this undergoes ring-closure when warmed with HCl or other condensing agents: [1]

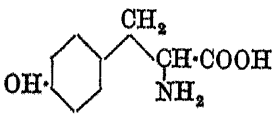


(30% yield).

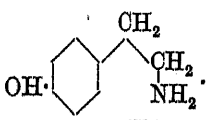
Phenylalanine,



gives a similar yield of tetrahydro*iso*quinoline-3-carboxylic acid, but much better results are obtained with tyrosine (I) and tyramine (II):

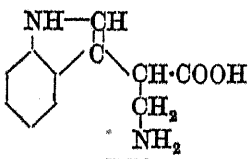


(I.)

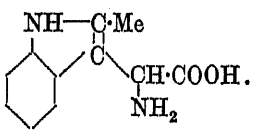


(II.)

The reaction fails with tryptophan *—a confirmation of Ellinger's formula (III), which has replaced the older formula (IV) of Hopkins and Cole:

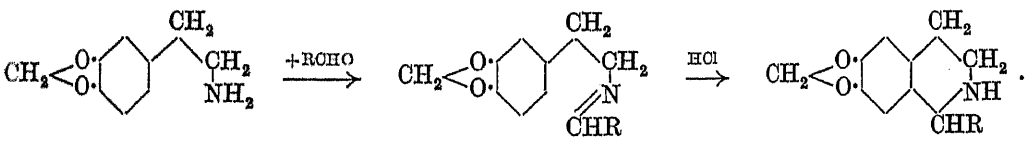


(III.)



(IV.)

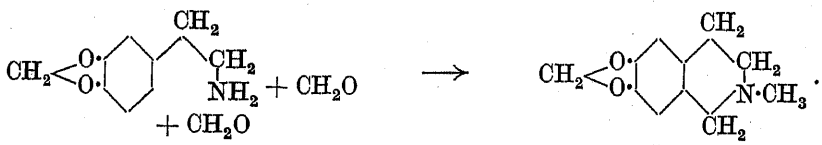
Decker and Becker [2] condensed homopiperonylamine (V) with a variety of aldehydes and converted the products into tetrahydro*iso*quinolines by the action of conc. HCl:



(V.)

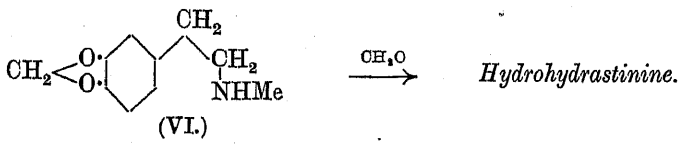
[1] Pictet and Spengler, *Ber.*, 1911, **44**, 2030; D.R.-P. 241425.
[2] *Ann.*, 1913, **395**, 346–362; D.R.-P. 257138.
* An example of failure to close an *iso*quinoline ring in a complex arylethylamine by means of methylal is mentioned on p. 311 (tetrahydrocolumbamine).

In the case of formaldehyde (R = H), under suitable conditions methylation may occur, leading directly to hydrohydrastinine : [1]



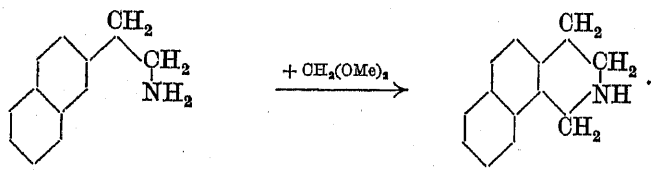
Hydrohydrastinine.

The same product is formed by the condensation of homopiperonylmethylamine (VI) with formaldehyde : [2]



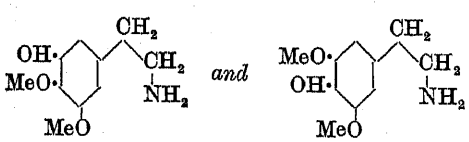
(VI.)

In the napthalene series Mayer and Schnecko [3] have obtained a tetrahydronaphth*iso*quinoline from β-naphthylethylamine and methylal :



The following arylethylamines have been converted into tetrahydro*iso*quinolines by condensation with aldehydes :

Arylethylamine.	*Aldehyde.*	*References.*
β-Phenylethylamine.	Formaldehyde.	1, 5, 11
N-Methylphenylethylamine.	Formaldehyde.	7
Phenylalanine.	Formaldehyde.	1, 5
Tyrosine.	Formaldehyde.	1, 3, 5
Tyramine.	Formaldehyde.	9
Homopiperonylamine.	Formaldehyde.	2, 4, 5, 6, 8
	Acetaldehyde.	6
	Benzaldehyde.	4, 6
	Cinnamaldehyde.	4, 6
	Piperonal.	4, 6
N-Methylhomopiperonylamine.	Formaldehyde.	4, 7



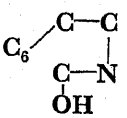
and	Formaldehyde.	10
β : β-Naphthylethylamine.	Formaldehyde.	12

[1] Decker and Becker, *loc. cit.*, p. 358.
[2] *Idem, loc. cit.*, p. 359; D.R.-PP. 281546, 281547.
[3] *Ber.*, 1923, **56**, 1408.

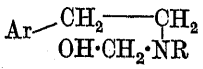
References.

[1] Pictet and Spengler, *Ber.*, 1911, **44**, 2030. [2] Pictet and Gams, *ibid.*, p. 2042. [3] Wellisch, *Biochem. Zeitschr.*, 1913, **49**, 173. [4] Decker and Becker, *Ann.*, 1913, **395**, 346–362. [5] D.R.-P. 241425 (Pictet). [6] D.R.-PP. 257138, 270859 (Decker). [7] D.R.-PP. 281546, 281547 (Decker). [8] D.R.-P. 320480. [9] Fränkel and Zeimer, *Biochem. Zeitschr.*, 1920, **110**, 234. [10] Späth and Röder, *Monatsh.*, 1922, **43**, 100, 102. [11] Kondo and Ochiai, *J. Pharm. Soc. Japan*, 1923, 313–319. [12] Mayer and Schnecko, *Ber.*, 1923, **56**, 1408.

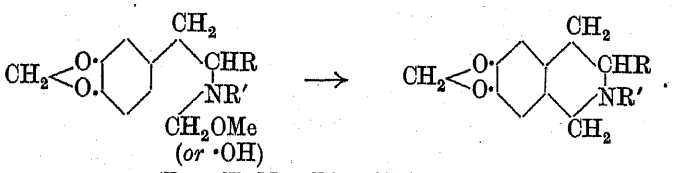
3. From methylol derivatives of β-arylethylamines:



This is simply a special case of the method discussed in the preceding section, the intermediate

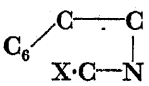


being isolated. Compounds of this type may be prepared by the action of chloromethyl ether, $ClCH_2{\cdot}OMe$, upon β-arylethylamines [1] and may be converted into *iso*quinolines by treatment with P_2O_5 [2] or 10% HCl at 100°: [3]

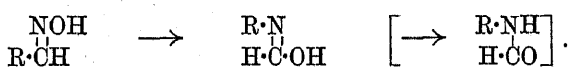


(R = H, Me; R′ = H, Me, Et.)

4. By Beckmann rearrangement of oximes:



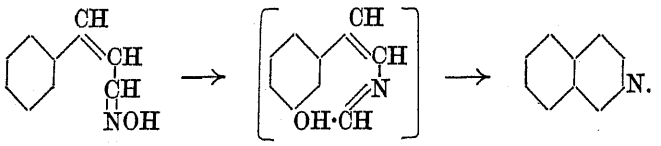
In the isomerisation of oximes by the action of PCl_5, etc., the enolic form of the acid amide is an intermediate product:



If the radical R contains a phenyl group in a suitable position condensation might be expected to occur with elimination of water and formation of an *iso*quinoline derivative. This was found

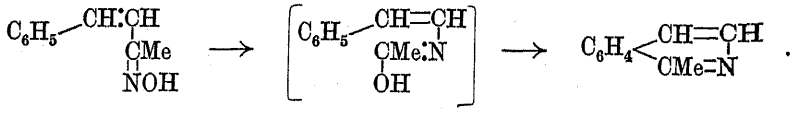
[1] D.R.-P. 273323. [2] D.R.-P. 280502.
[3] D.R.-P. 336153; see also Kaufmann and Dürst, *Ber.*, 1917, **50**, 1630.

actually to take place by Bamberger and Goldschmidt,[1] who obtained *iso*quinoline itself from cinnamaldoxime and P_2O_5:



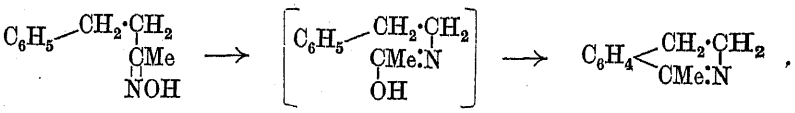
The yield was only about 10%.[2]

Zelinsky as early as 1887 [3] had obtained an oily base by the action of P_2O_5 upon the oxime of styryl methyl ketone (benzalacetone). This was shown by Goldschmidt [4] to be, not the expected 1-methyl*iso*quinoline, but the unsubstituted base. Burstin [5] succeeded, however, in obtaining the 1-methyl derivative from Zelinsky's oxime:



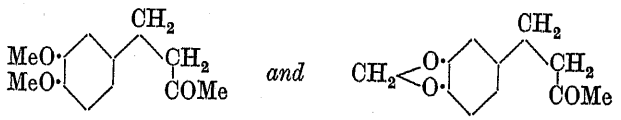
The corresponding 1-phenyl*iso*quinoline cannot be prepared in this way from benzalacetophenone.[6]

Saturated oximes give better results. Pictet and Kay [7] by the action of P_2O_5 in toluene upon the oxime of benzylacetone obtained a 48% yield of 1-methyl-3 : 4-dihydro*iso*quinoline:



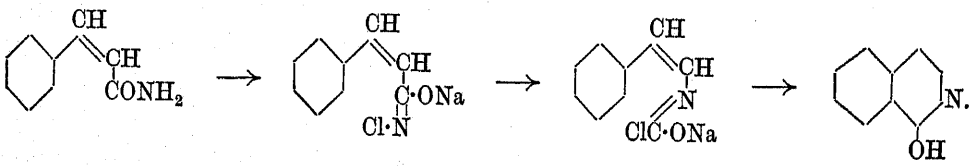
(The yield of the same product from acetylphenylethylamine was only 33%.)

Kaufmann and Radosević [8] have used the same method for the conversion of the oximes of



into dihydro*iso*quinolines.

Attempts have been made to apply the somewhat similar Hofmann reaction (conversion of amides into amines by NaOCl, etc.) to the synthesis of *iso*quinolines, but so far without success. Thus cinnamic amide might be expected, under suitable conditions, to give *iso*carbostyril:

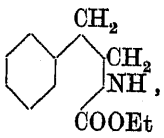


[1] *Ber.*, 1894, **27**, 1954.
[2] Goldschmidt, *ibid.*, p. 2795.
[3] *Ibid.*, 1887, **20**, 922.
[4] *Ibid.*, 1895, **28**, 818.
[5] *Monatsh.*, 1913, **34**, 1443.
[6] Goldschmidt, *Ber.*, 1895, **28**, 986.
[7] *Ibid.*, 1908, **41**, 1973.
[8] *Ibid.*, 1916, **49**, 675.

Unfortunately, the reaction fails with unsaturated amides.[1] Weerman and Jongkees [2] were equally unsuccessful with the corresponding saturated amide, the only product being β-phenylethylamine or, in the cold, the symmetrical urea,

$$(PhCH_2{\cdot}CH_2{\cdot}NH)_2CO,$$

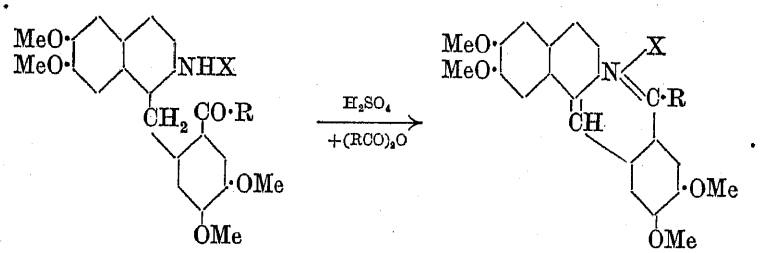
from which no dihydro*iso*carbostyril could be obtained. They were also unable to convert β-phenylethylurethane,



into dihydro*iso*carbostyril by the action of sodamide.

5. From *o*-β-aminoethylaryl ketones: $C_6<^{C\text{——}C}_{CO{\cdot}R\ NH}$

No simple synthesis of this type has been recorded, but the method has been used by Schneider [3] for the preparation of coralyn from acetopapaverine. Ring-closure occurs in the presence of sulphuric acid and acetic anhydride, the product being obtained in the form of sulpho-acetate:



(R = Me (coralyn) or Et.)

The reaction recalls the "acridination" of α-arylaminoanthraquinones (p. 000)—the ·NH· being here replaced by ·CH_2· and the nuclear *ortho*-·CH· by ·NH·.

6. From *o*-β-aminoethylbenzoic acids: $C_6<^{C\text{——}C}_{COOH\ NH_2}$

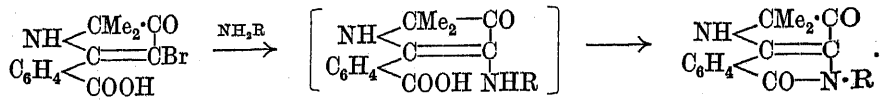
o-Carboxyphenylethylamine was prepared from tetrahydro*iso*quinoline by Bamberger and Dieckmann.[4] It is readily anhydrised to dihydro*iso*carbostyril:

$$C_6H_4<^{CH_2{\cdot}CH_2}_{CH_2{\cdot}N{\cdot}COPh} \xrightarrow{KMnO_4} C_6H_4<^{CH_2{\cdot}CH_2{\cdot}NH{\cdot}COPh}_{COOH} \xrightarrow{HCl}$$

$$C_6H_4<^{CH_2\text{——}CH_2}_{COOH\ NH_2} \longrightarrow C_6H_4<^{CH_2{\cdot}CH_2}_{CO\text{—}NH}.$$

[1] Hofmann, *Ber.*, 1888, **21**, 2695.
[2] *Rec. trav. chim.*, 1906, **25**, 238.
[3] Schneider and Schröter, *Ber.*, 1920, **53**, 1459; Schneider and Nitze, *ibid.*, 1923, **56**, 1036.
[4] *Ibid.*, 1893, **26**, 1217.

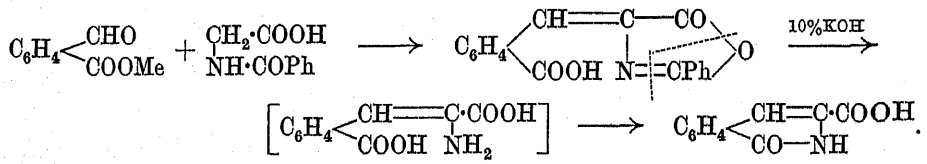
The synthesis of "gyrolone" and its *N*-methyl derivative [1] involves a similar type of ring-closure:



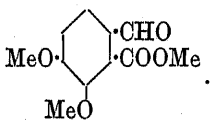
(R = H, Me.)

The same product may be obtained by introducing a nitro- or nitroso-group in place of the Br and reducing to amine.

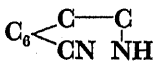
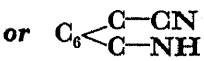
The synthesis devised by Bain, Perkin and Robinson [2] from hippuric acid and *o*-carboxy-aldehydes may be compared with the method of E.P. 191233 (p. 312):



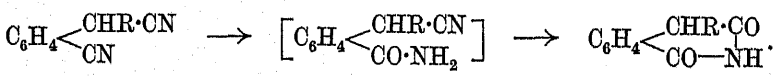
Methyl opianate (I) behaves in an analogous manner.



(I.)

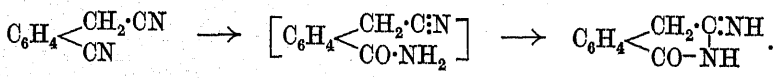
7. From *o*-cyanobenzyl cyanide etc.:  ***or*** 

o-Cyanobenzyl cyanide is the dinitrile of homophthalic acid and gives homophthalimide when hydrolysed with H_2SO_4: [3]



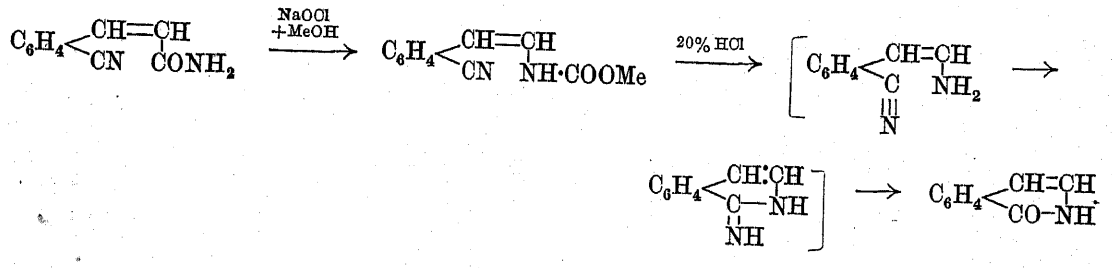
(R = H, Me, Et.)

That the nuclear ·CN is hydrolysed before the side-chain ·CN is shown by the formation of a 3-imino-derivative when alkali is used.[4]



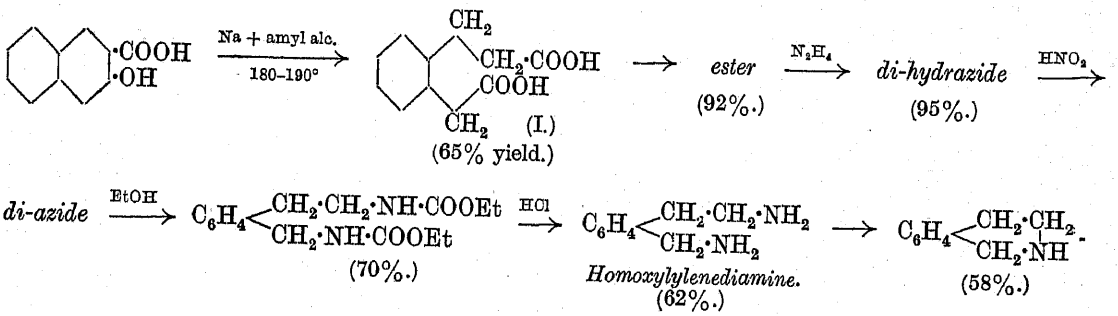
[1] Gabriel, *Ber.*, 1911, **44**, 72.
[2] *J. C. S.*, 1914, **105**, 2397.
[3] Gabriel, *Ber.*, 1887, **20**, 2499.
[4] Gabriel and Posner, *ibid.*, 1894, **27**, 836.

A closely related ring-closure is the preparation of *iso*carbostyril from *o*-cyanocinnamic amide :[1]



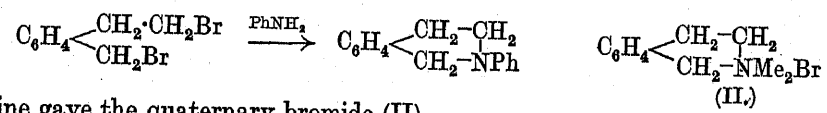
8. From homoxylylenediamines etc. : $C_6<^{C\cdot C\cdot NH_2}_{C\cdot NH_2}$

Homoxylylenediamine has recently been prepared in good yield from β-hydroxynaphthoic acid by Helfer.[2] The dihydrochloride gives a 58% yield of tetrahydro*iso*quinoline when distilled :



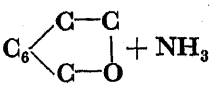
The acid (I) was also reduced and the hexahydro-derivative converted into decahydro*iso*quinoline.

v. Braun and Zobel[3] obtained a tetrahydro*iso*quinoline by the action of aniline upon homoxylylene dibromide :

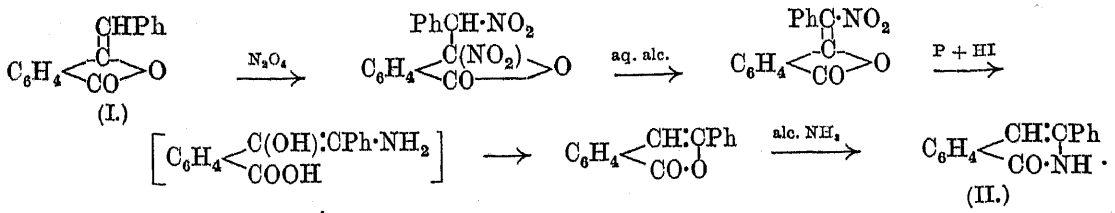


Dimethylamine gave the quaternary bromide (II).

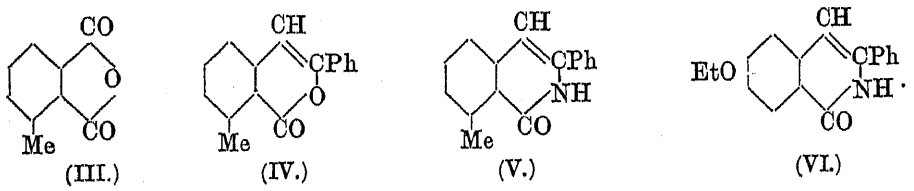
[1] Gabriel, *Ber.*, 1916, **49**, 1611. [2] *Helv. Chim. Acta*, 1923, **6**, 789. [3] *Ber.*, 1923, **56**, 2151, 2152.

9. From *iso*coumarin derivatives : 

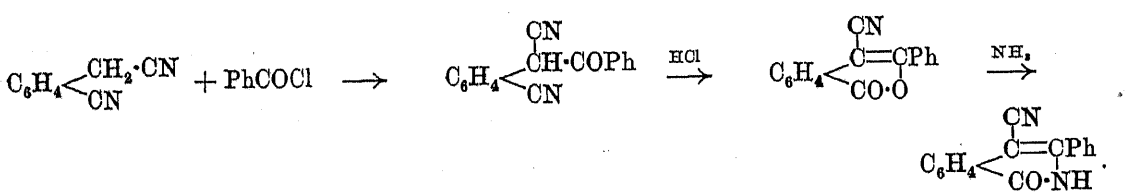
Benzalphthalide (I), prepared by the condensation of phthalic anhydride with phenylacetic acid in the presence of sodium acetate, forms a dinitro compound when treated with nitrous fumes, and this product is converted into "*iso*benzalphthalimidine" (II) by the successive action of dilute alcohol, P and HI and alcoholic ammonia. These reactions were studied by Gabriel,[1] who showed that the final product was 3-phenyl*iso*carbostyril (II) :



The *p*-tolyl compound was similarly prepared by Heilmann [2] and the *o*-anisyl compound by Bethmann,[3] but the condensation product of phthalic anhydride with acetic acid gives only a poor yield of unsubstituted *iso*coumarin and hence of *iso*carbostyril.[4] The method has been used by Müller [5] for the preparation of 3-phenyl-8-methyl*iso*coumarin (IV) and the corresponding *iso*carbostyril (V) from 3-methylphthalic anhydride (III), and by Onnertz [6] for 6(or 7)-ethoxy-3-phenyl*iso*carbostyril (VI).

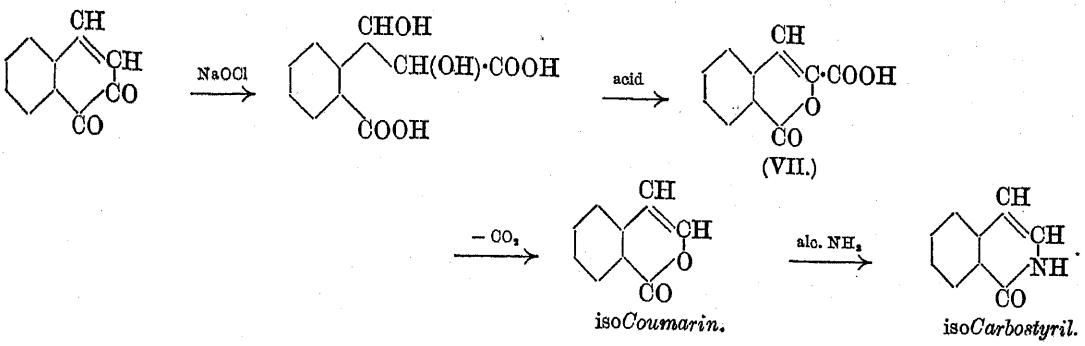


o-Cyanobenzyl cyanide was converted into an *iso*coumarin and hence into an *iso*carbostyril by Gabriel and Neumann : [7]



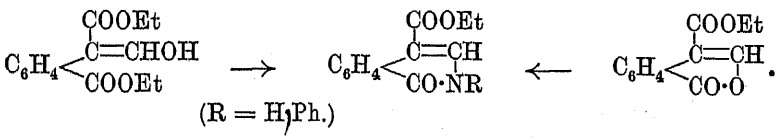
[1] *Ber.*, 1885, **18**, 1251, 2445, 3470; 1886, **19**, 830, 1653.
[2] *Ibid.*, 1890, **23**, 3162.
[3] *Ibid.*, 1899, **32**, 1111.
[4] Gabriel, *ibid.*, 1903, **36**, 573.
[5] *Ibid.*, 1909, **42**, 428.
[6] *Ibid.*, 1901, **34**, 3744.
[7] *Ibid.*, 1892, **25**, 3571; see also p. 320.

A much more convenient method for *iso*coumarin and *iso*carbostyril is from β-naphthaquinone : [1]

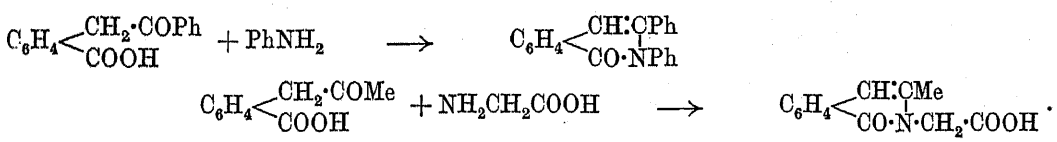


From the carboxylic acid (VII) Bamberger and Frew [2] obtained quantitative yields of *iso*carbostyrilcarboxylic acids by the action of methylamine, ethylamine and aniline.

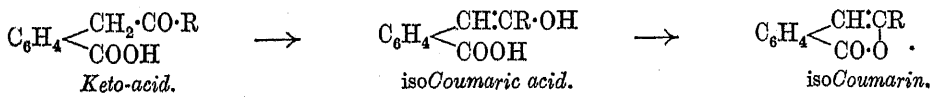
*iso*Coumaric esters give the same products as the corresponding *iso*coumarins : [3]



Similarly, *o*-phenacylbenzoic acid [4] and *o*-acetonylbenzoic acid [5] react with amines to give *iso*carbostyrils :



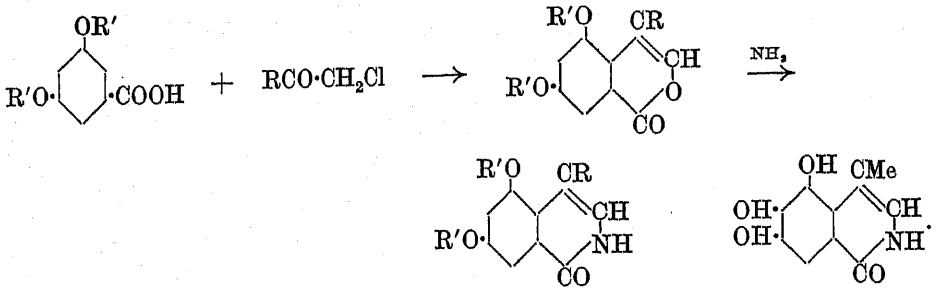
These keto-acids are simply ketonic forms of the *iso*coumaric acids :



The conversion of *iso*coumarins into *iso*carbostyrils is also described by Fritsch,[6] who obtained

[1] D.R.-P. 65947; Bamberger and Kitschelt, *Ber.*, 1892, **25**, 1138; Zincke, *ibid.*, p. 1493; Bamberger and Frew, *ibid.*, 1894, **27**, 208.
[2] *Loc. cit.*, p. 202.
[3] Dieckmann and Meiser, *ibid.*, 1908, **41**, 3253.
[4] Gabriel, *ibid.*, 1885, **18**, 2449.
[5] Gottlieb, *ibid.*, 1899, **32**, 966.
[6] D.R.-P. 73700.

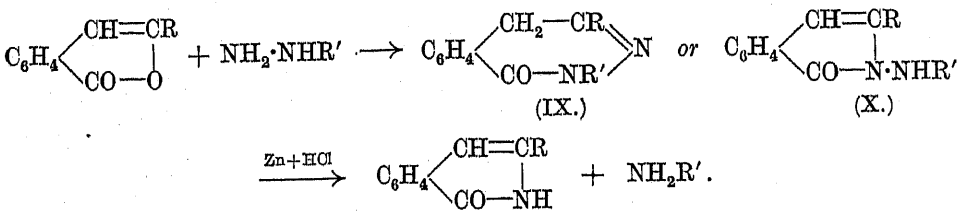
the former from α-resorcylic acid or its ethers by the action of chloroacetone or phenacyl chloride:



(R′ = H, Et; R = Me, Ph.) (VIII.)

A similar method leads to 5 : 6 : 7-trihydroxy-4-methyl*iso*carbostyril (VIII) from gallic acid.[1]

The action of hydroxylamine and hydrazines upon *iso*coumarins is said to give compounds containing a seven-membered ring (IX). The hydrazine products, however, readily lose NH_3 or NH_2Ph by reduction with Zn and HCl, and this is a strong indication that they are really *N*-amino-derivatives (X):



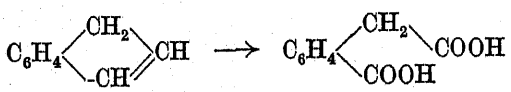
(IX.) (X.)

(R′ = H *or* Ph; R = Me, Et,[2] Ph,[3] *m*-C_7H_7.[4])

Lieck [5] claims to have obtained a small yield of *N*-amino-3-*m*-tolyl*iso*carbostyril (X, R = *m*-C_7H_7) by the action of HCl upon the hydrazine derivative (IX).

10. From homophthalic acids etc.: $C_6<^{C—COOH}_{COOH} + NH_2R$

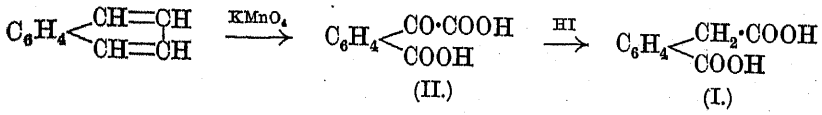
Homophthalic acid (I) may be prepared by oxidation of indene with $KMnO_4$



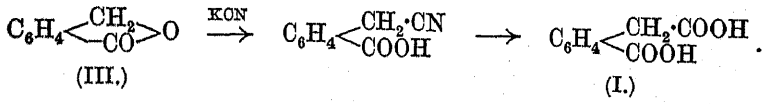
(I.)

[1] Fritsch, *Ber.*, 1893, **26**, 419.
[2] Gottlieb, *ibid.*, 1899, **32**, 966.
[3] Wölbling, *ibid.*, 1905, **38**, 3845.
[4] Lieck, *ibid.*, p. 3853.
[5] *Loc. cit.*

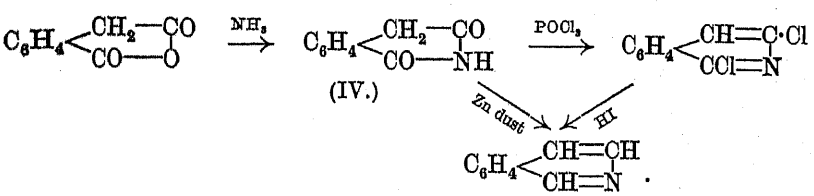
or by reduction of phthalonic acid (II) obtained by the oxidation of naphthalene



or from phthalide (III), and KCN followed by hydrolysis:

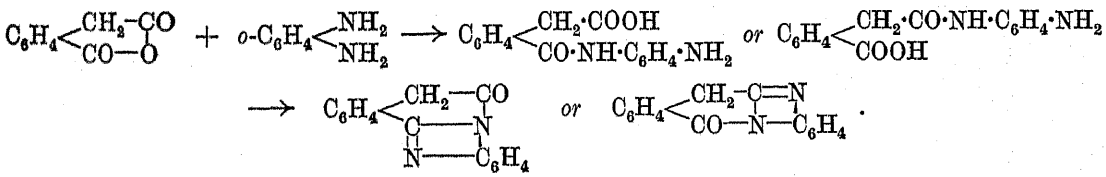


Homophthalimide (IV) is obtained easily by heating the ammonium salt of the acid or by the action of NH_3 upon the anhydride. It is reduced to *iso*quinoline by distillation with zinc dust [1] or by successive treatment with $POCl_3$ and HI.[2]

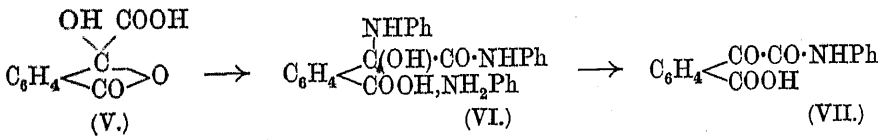


Dieckmann [3] prepared the *N*-phenyl- and *N*-benzyl-derivatives of homophthalimide by the action of aniline and benzylamine respectively upon the acid.

o-Phenylenediamine reacts with homophthalic anhydride to give first an anilide and at 200° an anhydro-derivative of the imide: [4]

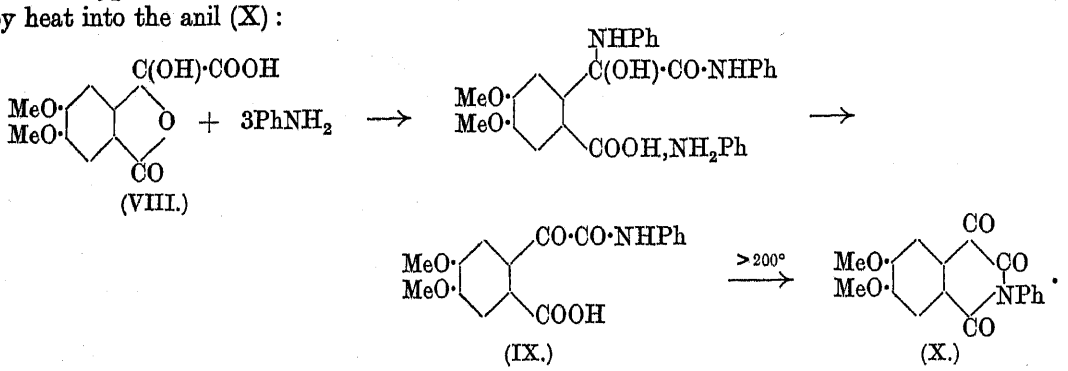


The anhydride of phthalonic acid, according to the recent researches of Kuroda and Perkin,[5] has the structure (V). It reacts with aniline in benzene solution to form the compound (VI), which when heated in chloroform gives the anilide (VII):



[1] Le Blanc, *Ber.*, 1888, **21**, 2299. [2] Gabriel, *ibid.*, 1886, **19**, 2354. [3] *Ibid.*, 1914, **47**, 1434.
[4] Bistrzycki and Fässler, *Helv. Chim. Acta*, 1923, **6**, 525. [5] *J. C. S.*, 1923, **123**, 2094.

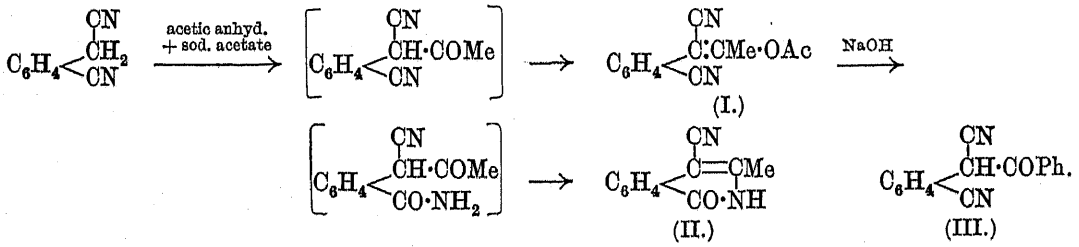
Dimethoxyphthalonic anhydride (VIII) similarly yields the anilide (IX), which may be converted by heat into the anil (X):



(VIII.) (IX.) (X.)

11. From *o*-cyanobenzyl ketones: $C_6<^{C(CO\cdot NH_2)}_{CH(CO\cdot R)}$

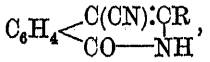
The methylene group in *o*-cyanobenzyl cyanide, being activated by the two adjacent negative radicles, is readily acylated by means of acid anhydrides or acid chlorides. Gabriel and Neumann [1] prepared a diacetyl derivative (I), from which by hydrolysis with alkali they obtained 3-methyl-4-cyano*iso*carbostyril (II):



(I.) (II.) (III.)

When acid is used for the hydrolysis the second nitrile group is lost as CO_2 and NH_3. Benzoyl chloride forms a *mono*benzoyl derivative (III), which may also be converted into an *iso*carbostyril (see p. 322).

The method has been employed for the preparation of the following *iso*carbostyrils, but the yields are only 20—30%:



where R =

	References.		*References.*
Methyl.	1, 2, 3	Butyl.	7
Ethyl.	4	Phenyl.	1, 2, 3
Propyl.	5	*p*-Tolyl.	6
*iso*Propyl.	7	*m*-Nitrophenyl.	6

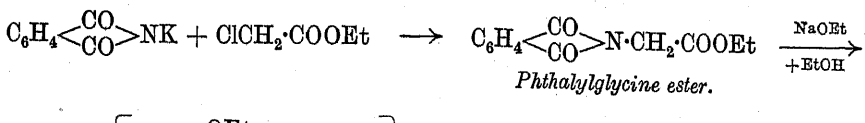
References.

[1] D.R.-P. 69138. [2] Gabriel and Neumann, *Ber.*, 1892, **25**, 3563. [3] Gabriel and Posner, *ibid.*, 1894, **27**, 827. [4] Damerow, *ibid.*, p. 2232. [5] Albahary, *ibid.*, 1896, **29**, 2391. [6] Harper, *ibid.*, p. 2543. [7] Lehmkuhl, *ibid.*, 1897, **30**, 889.

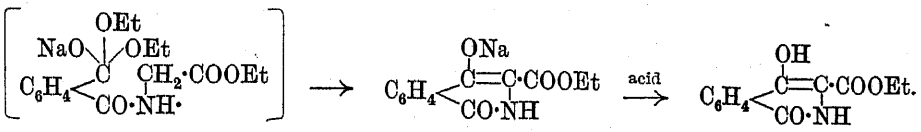
[1] *Ber.*, 1892, **25**, 3563.

12. From *N*-substituted phthalimides: $C_6<^{COOH\ CH_2}_{CO\text{——}NH}$

Phthalylglycine esters are condensed to *iso*quinoline derivatives by the action of NaOEt or NaOMe: [1]



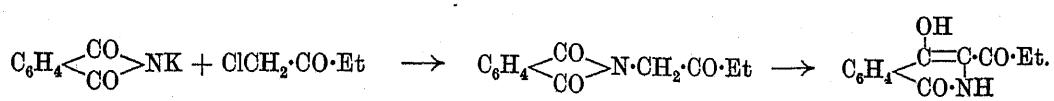
Phthalylglycine ester.



(65–75% yield.)

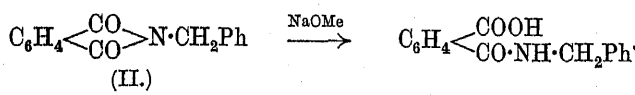
Sodium methoxide gives the corresponding methyl ester.

The reaction is restricted to carboxy-derivatives and to simple ketones such as phthalimino-methyl ethyl ketone (I): [2]



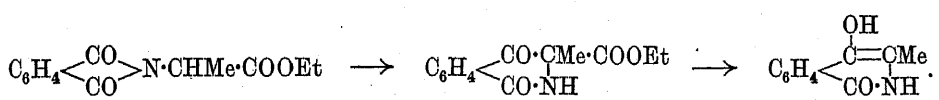
(I.)

Benzylphthalimide (II), for example, gives no *iso*quinoline derivative but only benzylphthalamic acid: [3]



(II.)

In the case of phthalyl derivatives of higher α-amino-acids the carbethoxy-group is lost during the reaction and the product is a 3-alkyl- or 3-aryl-1 : 4-dihydroxy*iso*quinoline:



Phthalylalanine.

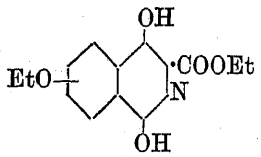
Gabriel and Colman in this way obtained the 3-methyl- and 3-ethyl-compounds, and Ulrich [4] the corresponding phenyl-,* *iso*propyl and *iso*butyl derivatives.

The phthalimino-esters were prepared either from potassium phthalimide and an α-chloro-ester or from phthalic anhydride and an α-amino-ester.

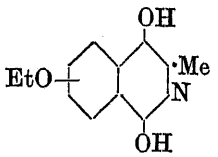
[1] Gabriel and Colman, *Ber.*, 1900, **33**, 980, 2630.
[2] Kolshorn, *ibid.*, 1904, **37**, 2485.
[3] Gabriel and Colman, *loc. cit.*
[4] *Ber.*, 1904, **37**, 1688.

* Since this derivative is not obtainable from benzylphthalimide, the carbethoxy-group must be lost *after* ring-closure as shown.

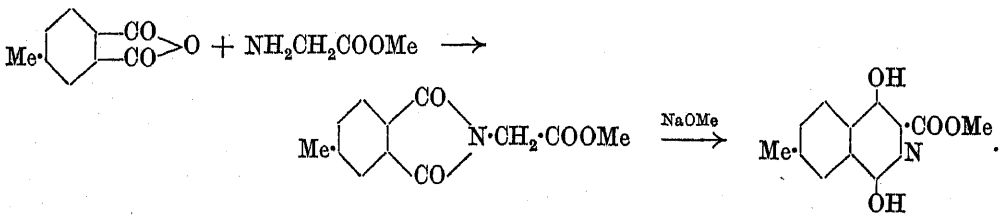
Küsel [1] condensed 4-ethoxyphthalic anhydride with glycine ester and with alanine ester and from the products obtained


(70% yield.)

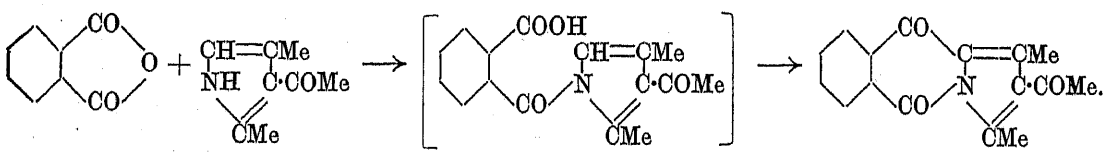
and


(45% yield.)

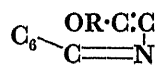
4-Methylphthalylglycine methyl ester was synthesised from *m*-toluidine by Findeklee [2] and gave the 1 : 4-dihydroxy-7-methyl*iso*quinoline-3-carboxylic ester (III) in 65% yield :


(III.)

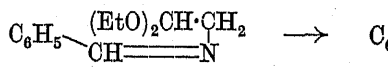
An interesting variant of the above reactions has been described by H. Fischer and Krollpfeiffer.[3] Any 2 : 3 : 4-trisubstituted pyrrole may be condensed with phthalic anhydride in glacial acetic acid at 180–190° to give a compound of the type (IV) :


(IV.)

Cryptopyrrole,* hæmopyrrole,* phonopyrrolecarboxylic acid * and 2 : 3 : 4-trimethylpyrrole behave in this way. Tetramethylpyrrole loses a methyl group and gives the same product as trimethylpyrrole.

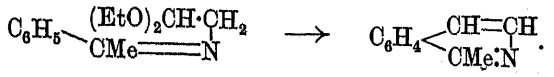
13. From benzalamino-acetals etc. : C_6 

By the action of $POCl_3$ or conc. H_2SO_4 upon benzalamino-acetal, *iso*quinoline is obtained in about 50% yield : [4]



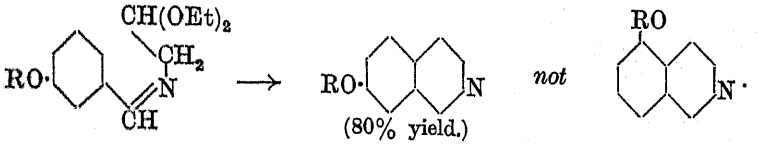
[1] *Ber.*, 1904, **37**, 1971. [2] *Ibid.*, 1905, **38**, 3542. [3] *Z. physiol. Chem.*, 1912, **82**, 266.
[4] Pomeranz, *Monatsh.*, 1893, **14**, 116; 1894, **15**, 299; Fritsch, *Ber.*, 1893, **26**, 421; D.R.-P. 80044.
* Formulæ for these compounds are given on p. 73.

The condensation product from acetophenone and aminoacetal gives a much smaller yield (15%) of 1-methyl*iso*quinoline :



Pomeranz [1] similarly prepared *iso*quinolines from aminoacetal and *o*- and *p*-tolualdehydes, *o*-chlorobenzaldehydes and benzophenone.

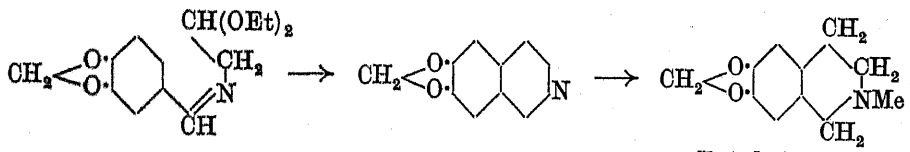
In the case of *meta*-substituted aldehydes ring-closure occurs *para* rather than *ortho* to the directing group : [2]



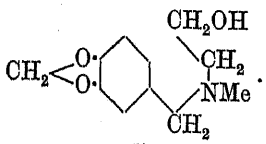
(80% yield.)

(R = H, Me, Et.)

The 6 : 7-methylenedioxy*iso*quinoline obtained in 24% yield from piperonal and aminoacetal may be converted into hydrohydrastinine by reduction and methylation : [3]

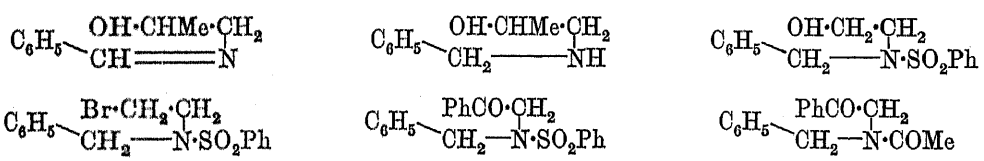


Hydrohydrastinine.



(I.)

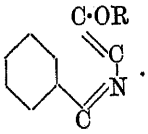
Hydrohydrastinine cannot be obtained directly from the saturated alcohol (I).[4] In this connection Staub [5] has made an interesting study of the action of condensing agents upon the following compounds :



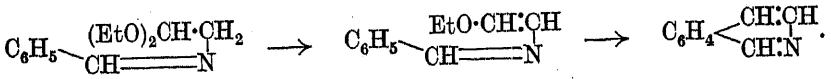
from none of which could *iso*quinoline derivatives be prepared. He suggests that ring-closure in such cases can only occur if the side-chain contains (*a*) conjugated double bonds (actual or

[1] *Monatsh.*, 1897, **18**, 1–5.
[2] Fritsch, *Ann.*, 1895, **286**, 12–15.
[3] *Idem, loc. cit.*, p. 15; D.R.-PP. 85566, 86561; D.Pat. Anm. F. 7830.
[4] Kaufmann and Dürst, *Ber.*, 1917, **50**, 1630.
[5] *Helv. Chim. Acta*, 1922, **5**, 888.

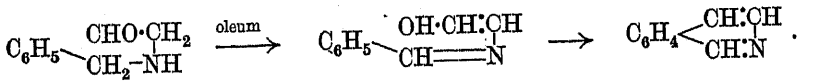
potential) and also (*b*) a group ·OH or ·OAlk β to the nitrogen atom, *i.e.* in compounds of the type



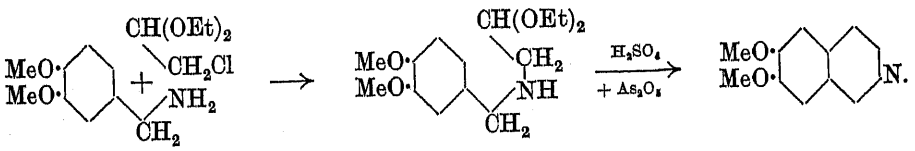
In the Pomeranz-Fritsch syntheses an ethoxymethylene compound is formed before ring-closure:



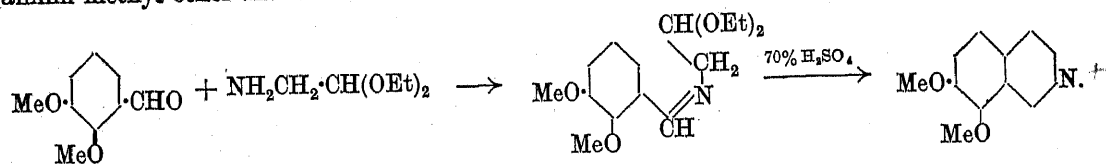
E. Fischer's synthesis of *iso*quinoline from benzylaminoacetaldehyde [1] is no exception to this rule, since the oleum used oxidises the benzyl- to a benzal-derivative:



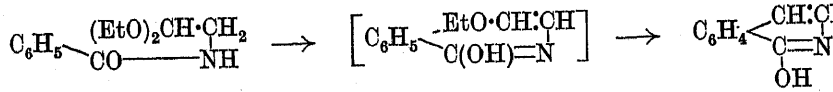
Rügheimer and Schön [2] used As_2O_5 as an oxidant in the preparation of 6 : 7-dimethoxy-*iso*quinoline:



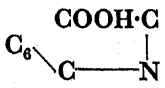
The isomeric 7 : 8-dimethoxy*iso*quinoline was obtained by Perkin and Robinson [3] from *ortho*-vanillin methyl ether and aminoacetal:



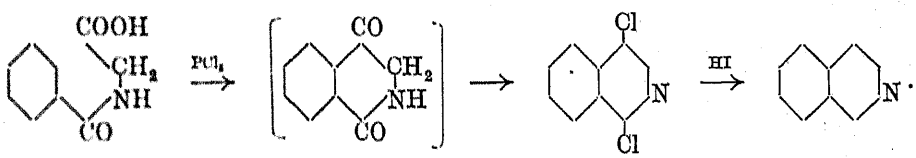
*iso*Carbostyril is formed in a similar manner from benzoylaminoacetal: [4]



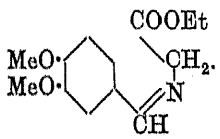
[1] *Ber.*, 1893, **26**, 764.
[2] *Ibid.*, 1909, **42**, 2374.
[3] *J. C. S.*, 1914, **105**, 2376.
[4] Fritsch, *Ber.*, 1893, **26**, 421.

14. From hippuric acid: 

The condensation products of hippuric acid with aldehydes have already been mentioned (pp. 312, 320) as a source of *iso*quinolines and of the phenylacetic acids required as intermediates in certain cases. Hippuric acid itself (benzoylglycine) is converted by PCl_5 into a dichloro-anhydro-compound from which *iso*quinoline is obtained by reduction with HI:[1]

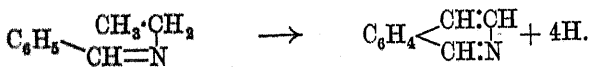


Perkin and Robinson[2] failed, however, to obtain an *iso*quinoline from 3:4-dimethoxy-benzalglycine ester

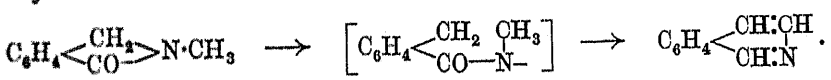


15. Pyrogenous methods:

Benzalethylamine passed through a hot tube gives appreciable quantities of *iso*quinoline together with a di*iso*quinolyl of unknown constitution:[3]

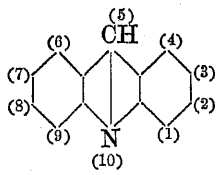


Graebe and Pictet[4] by distillation of *N*-methyl*iso*indolinone with zinc dust obtained a very small quantity of an oil, which Pictet[5] later identified as *iso*quinoline:



[1] Rügheimer, *Ber.*, 1886, **19**, 1172.
[2] *J. C. S.*, 1914, **105**, 2376.
[3] Pictet and Popovici, *Ber.*, 1892, **25**, 733.
[4] *Ann.*, 1888, **247**, 304.
[5] *Ber.*, 1905, **38**, 1949.

CHAPTER X

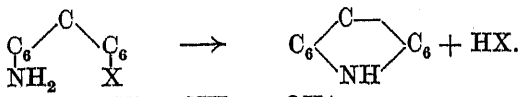
ACRIDINES, 

Introductory :

ALTHOUGH a very large amount of attention has been devoted to the preparation of acridine compounds (especially such as contain auxochromic groups and are therefore dyestuffs), only a few types of synthesis have been evolved since in all cases it is the *meso* ring which is closed. The synthetic methods available may be grouped as follows :

I. *From diphenylmethane derivatives :*

In this group (sects. 1–10) the most important method consists in the elimination of NH_3 from an *o* : *o'*-diamine or of H_2O from an *o* : *o'*-hydroxy-amine :



(I.) (X = ·NH_2 *or* ·OH.)

Examples of this type are very numerous and have been subdivided according to the method by which the required intermediate is prepared.

Aldehydes may be condensed with *m*-diamines (sect. 1), with *p*-substituted arylamines * (sect. 2), with *β*-naphthol and an arylamine (sect. 3) or with resorcinol and *p*-substituted arylamines (sect. 4). Phthalic anhydride behaves similarly with *m*-diamines (sect. 5). Alternatively an *o*-amino-carbinol or -carbinyl chloride may be condensed with a *m*-aminophenol, a *m*-dihydroxy-compound or a *β*-naphthol (sects. 4 and 6). The essential in all these cases is that the methane carbon atom provided by the aldehyde or the carbinol shall be forced into a position *ortho* to the ·NH_2 or ·OH—hence the necessity for using a *m*-diamine or a *p*-substituted arylamine. The method of section 3 is exceptional in that *ortho* substitution occurs even with *o*-toluidine and *α*-naphthylamine. In each of these reactions the product is a *dihydroacridine*, which is more or less easily converted into an *acridine* by oxidation with air, $FeCl_3$, nitrous acid, etc. *Acridones* result when an *o*-amino-*o*-hydroxybenzophenone is used (sects. 4 and 5).

The ethereal oxygen of fluorescein is replaceable by ·NH· by the action of ammonia under pressure, giving an *acridine* (sect. 7), and *decahydroacridines* are obtainable from the *o* : *o'*-dihydroxy-compound prepared by condensing dihydroresorcinol with formaldehyde (sect. 7).

o : *o'*-Dichloro-derivatives have only been used as a source of *acridones* in the anthraquinone series (sect. 8).

The investigation of the dyestuff, Phosphine, obtained as a by-product in the manufacture of Magenta, led to the synthesis of similar *acridines* by the oxidation of *o*-aminodiphenylmethanes or the reduction of the corresponding *o*-nitro-compounds (sect. 9).

The conversion of *o*-aminotriphenylcarbinol into 5-*phenylacridine* by gentle heating is somewhat unexpected (sect. 10).

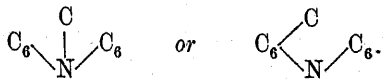
* Including *β*-naphthylamine.

II. *From benzyl- and benzal-anilines :*

Acridine itself is conveniently prepared by passing benzylaniline through a hot tube (sect. 11). A similar reaction leads to *chrysidines*, and the investigations of Grandmougin have shown that the synthesis of *Rheonines* must be regarded as analogous with these (sect. 11).

III. *From diphenylamines :*

This group of syntheses (sects. 12–21) may be subdivided according as the *meso* carbon atom is supplied by a substituent carried by the nitrogen or by a group in the *ortho* position



To the former class belong Bernthsen's synthesis from acyldiphenylamines (sect. 12) and the similar method from formanilides and *m*-diamines or *p*-substituted arylamines (sect. 13), both of which lead directly to *acridines*.

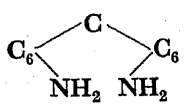
The conversion of arylanthranilic acids into *acridones* (sect. 14) is the most important example of the second class, and has been widely employed, not only for ordinary acridones, but also for naphthacridones and anthracridones. *o*-Arylamino-aldehydes (sect. 15) and -ketones (sect. 16) are largely used for *acridines*, especially in the anthraquinone series. It is not clear whether Stollé's oxalyl chloride method (sect. 16) should be considered as a modification of the Bernthsen synthesis or as an *ortho*-ketone acridination—probably the latter view is correct. *N*-Anthraquinonylisatins may be converted either into *anthracridines* (as with other arylisatins, sect. 16) or *anthracridones* (sect. 17), according to the strength of the H_2SO_4 employed.

A modification of the " *acridonation* " reaction (sect. 14) of value in the anthraquinone series is the use of *o*-arylamino-nitriles (sect. 18) in place of acids.

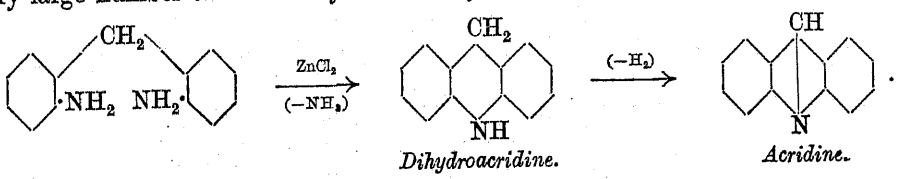
The tendency to ring-closure with formation of acridines is so marked that *acridines* are produced by dehydrogenation of *o*-methyldiphenylamines (sect. 19). Kehrmann's new synthesis of *dihydroacridines* from *o*-aminotriarylmethanes and di- or tri-nitrochlorobenzene (sect. 20) involves the elimination of HNO_2. It is of limited application.

Finally, *acridines* are obtained as by-products in Ullmann's carbazole synthesis if the arylaziminobenzene contains an *ortho* methyl group (sect. 21).

1. From *m*-diamines and aldehydes:

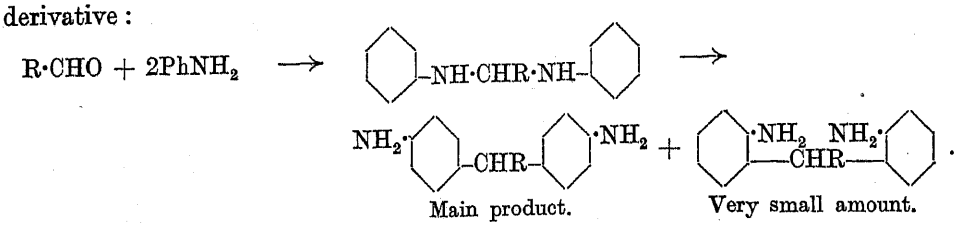


A very large number of acridine syntheses may be represented generally by the equations :



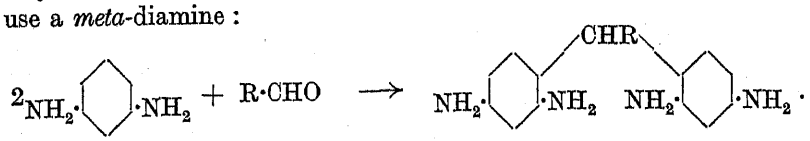
Dihydroacridine. *Acridine.*

Now when an aldehyde is condensed with an amine of the benzene series there is little tendency for the methylene group to take up the *ortho* position, the product being almost entirely the *para* derivative :

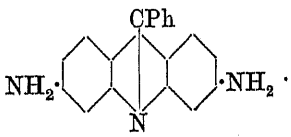


Main product. Very small amount.

The simplest way of ensuring that the product shall contain amino groups *ortho* to the aldehyde residue is to use a *meta*-diamine :

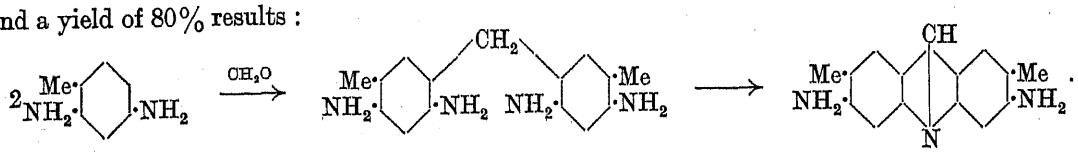


The earliest synthesis of this type was the preparation of Benzoflavine from benzaldehyde and *m*-phenylenediamine : [1]



Benzoflavine.

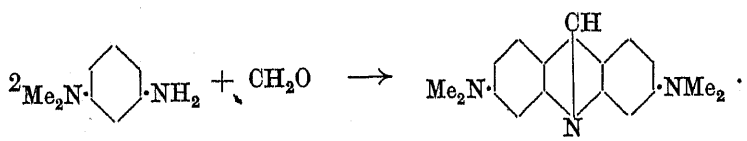
The use of other aromatic aldehydes with *m*-phenylene- and *m*-tolylene-diamines is described in D.R.-PP. 45294 and 45298. From formaldehyde and *m*-tolylenediamine the well-known Acridine Yellow is obtained.[2] In this case HCl under pressure is more effective than $ZnCl_2$, and a yield of 80% results :



Acridine yellow.

Acetaldehyde gives, less easily, a similar dyestuff.[3]

When *m*-aminodialkylanilines are used, the aldehyde condensation occurs *para* to the *substituted* amino group, and acridination follows normally. Acridine Orange NO is thus obtained from *m*-aminodimethylaniline,[4] and many other mono- and di-alkylated *m*-diamines have been employed : [5]

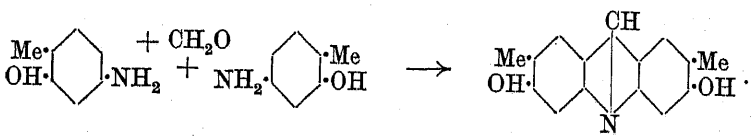


Acridine orange NO.

[1] D.R.-PP. 43714, 43720; Meyer and Gross, *Ber.*, 1899, **32**, 2352.
[2] D.R.-PP. 52324, 136617; Ullman and Marié, *Ber.*, 1901, **34**, 4307; Haase, *ibid.*, 1903, **36**, 588; Ullmann and Fitzenkam, *ibid.*, 1905, **38**, 3794. [3] D.R.-P. 143893. [4] D.R.-P. 59179.
[5] D.R.-PP. 67609, 70935, 133709, 141297.

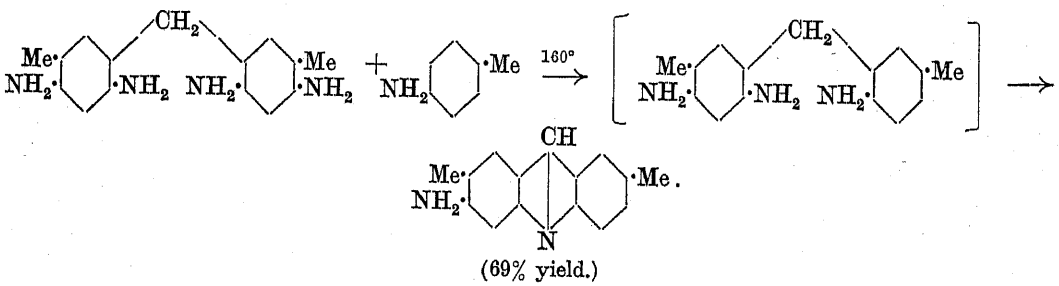
The condensation of formaldehyde with a mixture of two *m*-diamines and the conversion of the *products* into unsymmetrical acridines is described in D.R.-P. 133709. Methylation and acridination may be brought about in one operation by heating the tetra-aminodiphenylmethane with methyl alcohol and HCl at 150–160° [1] or with HCl and chloroacetic acid, which methylates by loss of CO_2.[2] The symmetrical dibenzyl derivative of Acridine Yellow is obtained from *p*-amino-benzyl-*o*-toluidine and formaldehyde.[3]

By the action of conc. H_2SO_4 at 180–200° one or both amino groups may be hydrolysed to ·OH during acridination, the yield of dihydroxyacridine being about 64%.[4] Dihydroxydimethylacridine is also obtained from *p*-amino-*o*-cresol : [5]



From *m*-aminodimethylaniline and benzaldehyde Acridine Orange R is prepared,[6] and similar condensations of aromatic aldehydes with *m*-diamines are claimed in D.R.-PP. 70065, 71362, 94951 and 102072.

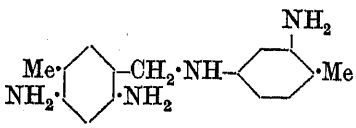
Terrisse and Darier [7] discovered that *p*-toluidine displaces one equivalent of a *m*-diamine from its condensation product with formaldehyde, and acridination follows, giving a *mono*-aminoacridine :



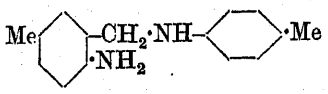
(69% yield.)

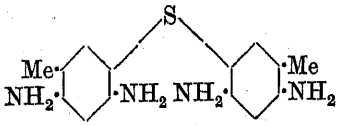
Apparently any combination of either of the two bases with formaldehyde leads to the same product under suitable conditions. Thus the above compound, 2-amino-3 : 7-dimethylacridine, is obtainable from

 and *p*-toluidine [8]

 and *p*-toluidine [9]

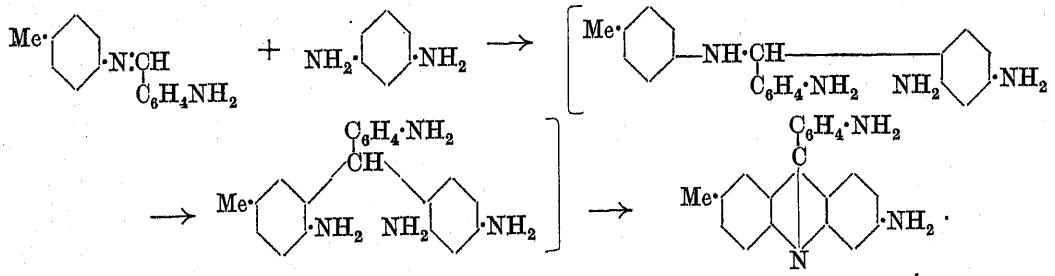
[1] D.R.-P. 129479. [2] D.R.-P. 133788. [3] D.R.-P. 141297.
[4] D.R.-P. 121686; Ullmann and Fitzenkam, *Ber.*, 1905, **38**, 3794.
[5] D.R.-P. 120466. [6] D.R.-P. 68908.
[7] D.R.-P. 107517; see also Ullmann, *Ber.*, 1903, **36**, 1017; Fox and Hewitt, *J. C. S.*, 1904, **85**, 531.
[8] D.R.-P. 107517. [9] D.R.-P. 118076.


and *m*-tolylenediamine [1]

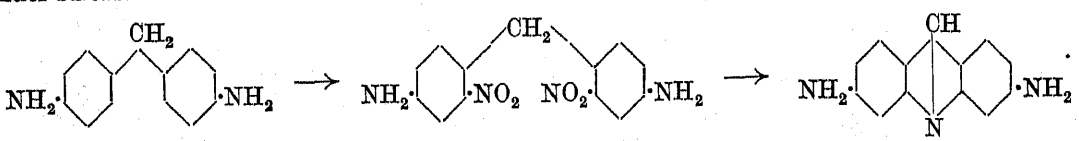

and the methane base [2] (see p. 334).

The benzaldehyde condensation products behave similarly.

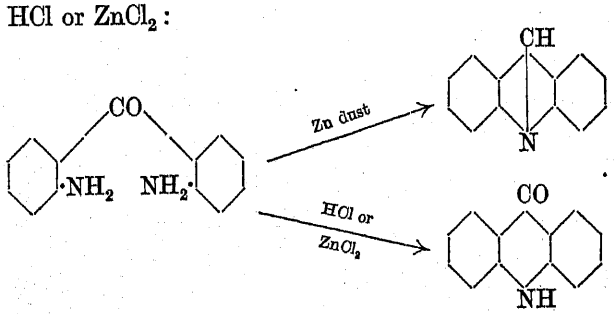
In a further modification of the Terrisse-Darier synthesis *p*-aminobenzal-*p*-toluidine is heated with *m*-phenylenediamine : [3]



Another method of introducing the *ortho* amino groups is by dinitration and reduction of the diamino-diphenylmethane. When the *o* : *o'*-dinitro-derivative is treated with $SnCl_2$ and HCl at 135° reduction is followed at once by acridination.[4] The product is usually a mixture of acridine and dihydroacridine, though the amount of the latter may be reduced considerably under suitable conditions.

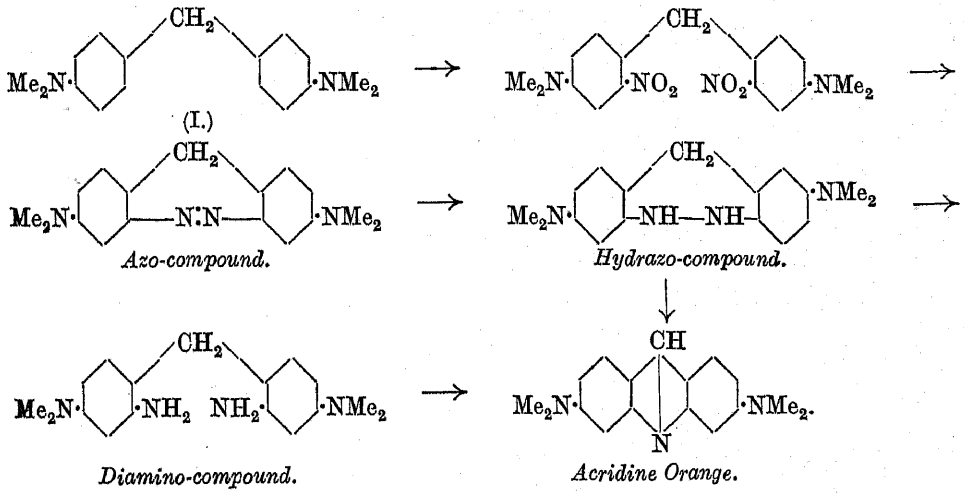


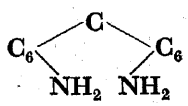
Tetranitration and reduction of diphenylmethane gives a 2 : 8-diaminoacridine.[5] Schöpf [6] found it more convenient to oxidise the tetranitrated diphenylmethane to tetranitrobenzophenone, which was converted by $SnCl_2$ and HCl into diaminoacridone. Staedel [7] prepared *o* : *o'*-diamino-benzophenone, from which he obtained acridine by distillation with zinc dust or acridone by treatment with conc. HCl or $ZnCl_2$:



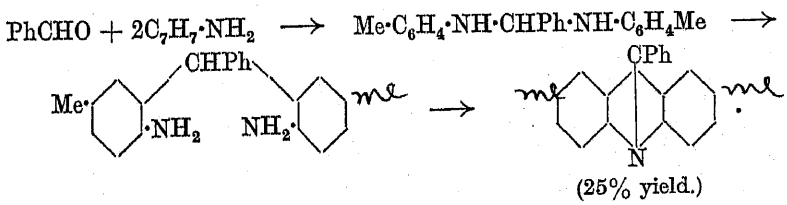
[1] D.R.-P. 107626. [2] D.R.-P. 288841. [3] D.R.-P. 106719.
[4] D.R.-P. 230412; Benda, *Ber.*, 1912, **45**, 1791; Moudgill, *J. C. S.* 1922, **121**, 1506.
[5] Gram, *Dissn. Jena*, 1892. [6] *Ber.*, 1894, **27**, 2316. [7] *Ibid.*, p. 3362.

The " methane base " (I) from dimethylaniline and formaldehyde was dinitrated and reduced to azo-, hydrazo- and diamino-derivatives by Duval.[1] Both the hydrazo- and the diamino-compounds are converted by conc. HCl into Acridine Orange :



2. From *p*-substituted amines and aldehydes : 

In the condensation of an aldehyde with an aromatic amine in which the *para* position is occupied, the entrant group is forced into the *ortho* position, and the product can be converted into an acridine by suitable treatment. Thus Ullmann [2] prepared 3 : 7-dimethyl-5-phenyl-acridine from *p*-toluidine and benzaldehyde :



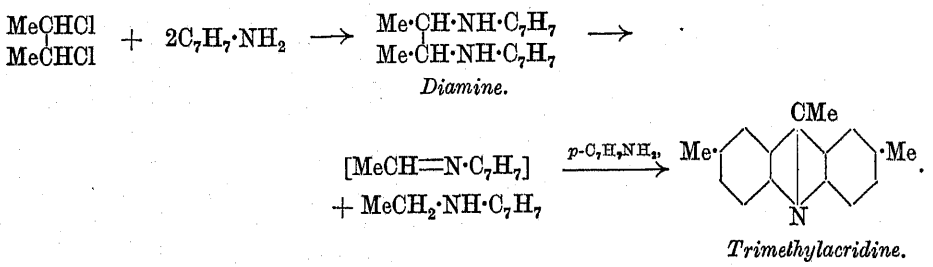
(25% yield.)

The method is general and can be used with aliphatic or aromatic aldehydes and with any *para* substituted aromatic amine.[3] The methane base may be acridinated without the use of $ZnCl_2$ by simply heating to 200–220° with *p*-toluidine hydrochloride. From formaldehyde, *p*-toluidine and *p*-toluidine hydrochloride, dimethylacridine and its dihydro derivative are obtained in equal amounts (total yield 69%).

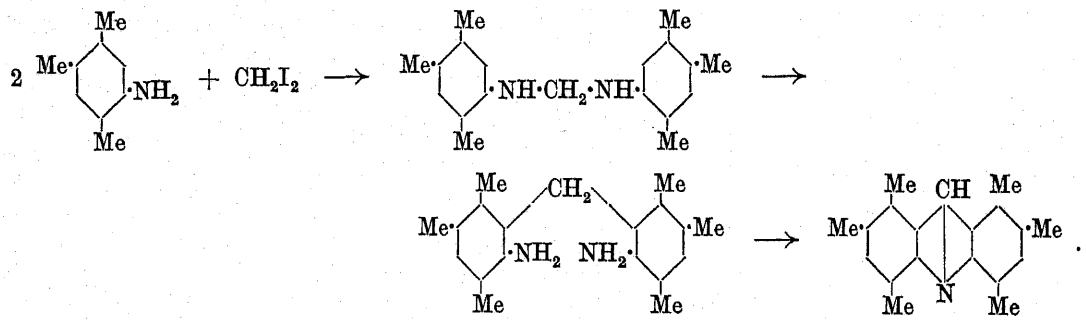
[1] *Bull. Soc. chim.*, 1910, [iv], **7**, 485. [2] *J. pr. Chem.*, 1887, **36**, 246.
[3] Ullmann, *Compt. rend. Soc. de Chim. de Geneve*, June 1898; *Ber.*, 1903, **36**, 1017.

m-Xylidine and benzaldehyde give only a poor yield of tetramethylphenylacridine. *p*- and *m*-Nitrobenzaldehydes have also been used with *p*-toluidine.

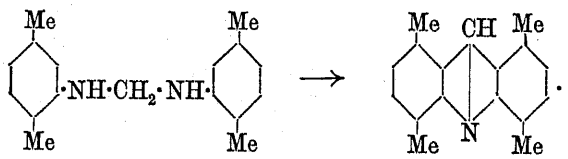
A reaction which must be classed with these is the formation of 3 : 5 : 7-trimethylacridine by the interaction of $\beta : \gamma$-dichlorobutane and *p*-toluidine.[1] The product is a mixture of the expected *dl*- and *meso*-diamines and the acridine. The latter may be obtained by heating the diamine hydrochloride with *p*-toluidine, or from acetaldehyde and *p*-toluidine. A possible mechanism is the following :



Senier and Goodwin [2] found that methylene diiodide gave with aniline, toluidines or xylidines only a methylenediamine, but with ψ-cumidine, in the presence of K_2CO_3 at 150–160°, hexamethylacridine :

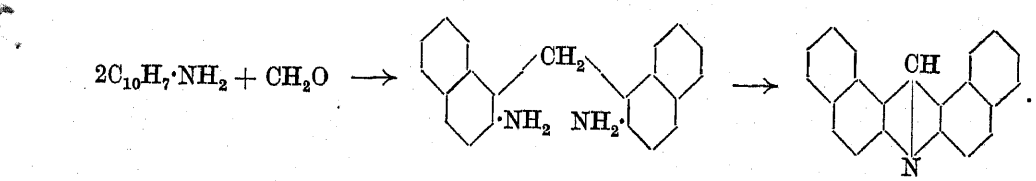


Senier and Compton [3] used both CH_2Cl_2 and CH_2I_2 for the preparation of acridines from *m*-xylidine and ψ-cumidine. They were also able to prepare 1 : 4 : 5 : 8-tetramethylacridine by heating di-*p*-xylyl-methylenediamine with *p*-xylidine and its hydrochloride,[4] though here the position *para* to the NH_2 group is unoccupied :

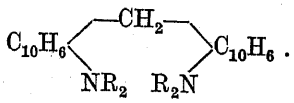


[1] Morgan and Hickinbottom, *J. C. S.*, 1923, **123**, 99, 104.
[2] *Ibid.*, 1902, **81**, 285.
[3] *Ibid.*, 1907, **91**, 1929, 1934.
[4] *Ibid.*, p. 1933.

In the naphthalene series *o* : *o'*-diamino-methane bases are readily prepared. Reed [1] first obtained a dinaphthacridine as a by-product in the condensation of β-naphthylamine with methylal and acetone in the presence of HCl. The same base was prepared by Morgan [2] from β-naphthylamine and formaldehyde in acidified alcoholic solution :



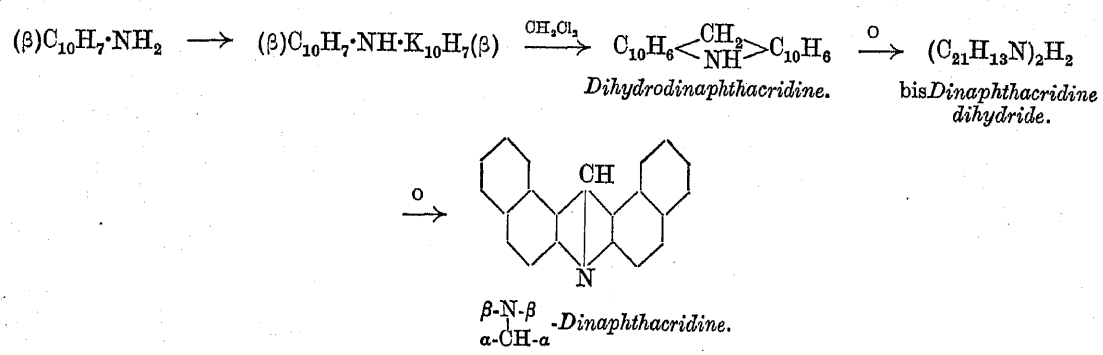
Ethyl-β-naphthylamine reacts similarly, giving 10-ethyldihydroacridine, but with dialkyl-β-naphthylamines no ring-closure takes place and the product is



α-Naphthylamine gives no acridine with formaldehyde,[3] but from naphthionic acid an α-dinaphthacridine-disulphonic acid may be prepared. Brönner acid (2 : 6-naphthylaminesulphonic) behaves normally.

Haase [4] obtained almost quantitative yields of β-dinaphthacridines from β-naphthylamine and benzaldehyde or *m*- and *p*-nitrobenzaldehydes. The *ortho*-nitro-aldehyde failed under all conditions.

Senier and Goodwin [5] showed that methylene diiodide may with advantage replace formaldehyde, and condenses readily with both α- and β-naphthylamines. Methylene dichloride reacts even more easily than CH_2I_2.[6] Senier and Austin represent the reaction as follows :



Dihydrodinaphthacridine. bis*Dinaphthacridine dihydride.*

β-N-*β*
α-CH-*α* *-Dinaphthacridine.*

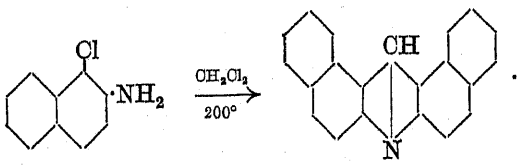
By varying the conditions in the case of $PhCHCl_2$ and β-naphthylamine, they were able to isolate

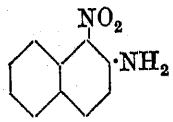
[1] *J. pr. Chem.*, 1886, **34**, 160; 1887, **35**, 314.
[2] *J. C. S.*, 1898, **73**, 536; see also Möhlau and Haase, *Ber.*, 1902, **35**, 4164.
[3] *Idem, ibid.*, p. 4173. [4] *Ibid.*, 1903, **36**, 591.
[5] *J. C. S.*, 1902, **81**, 288. [6] Senier and Austin, *ibid.*, 1906, **89**, 1387.

di-β-naphthylamine from the product, and in the case of CH_3CHCl_2 the reaction does not go beyond this stage.* Hydrides are not formed from α-naphthylamines.

Somewhat unexpected differences are observed in the behaviour of various aldehydes and the corresponding dihalides. α-Naphthylamine gives acridines with benzaldehyde, *o*-, *m*- and *p*-tolualdehydes, *o*- and *p*-anisaldehydes and *m*-nitrobenzaldehyde, but not with aliphatic aldehydes. CH_2Cl_2 and $CHMeCl_2$, on the other hand, react with α-naphthylamine more or less readily. From β-naphthylamine acridines are obtained by condensation with HCHO, CH_2Cl_2, PhCHO and $PhCHCl_2$, but not with *p*-anisaldehyde or *p*-tolualdehyde. No acridines resulted when salicylaldehyde, *p*-hydroxybenzaldehyde, vanillin or piperonal are made to react with α- or β-naphthylamine.

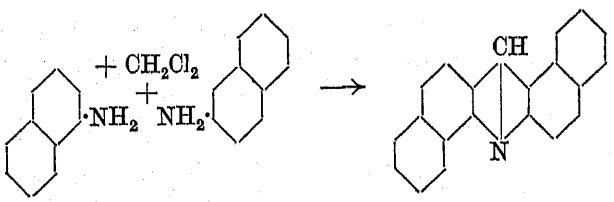
Attempts to obtain a " linear " dinaphthacridine have been unsuccessful.[1] If the α-position in the β-naphthylamine used is occupied by an easily eliminated radicle (*e.g.* Cl) it is displaced. If the α-group is not easily eliminated no condensation occurs :





gives no naphthacridine.

A mixture of α- and β-naphthylamines condenses with CH_2Cl_2 or CH_2I_2 (but not with benzal chloride) to give an unsymmetrical $\begin{pmatrix}\alpha\text{-N-}\beta\\ \beta\text{-CH-}\alpha\end{pmatrix}$ dinaphthacridine :

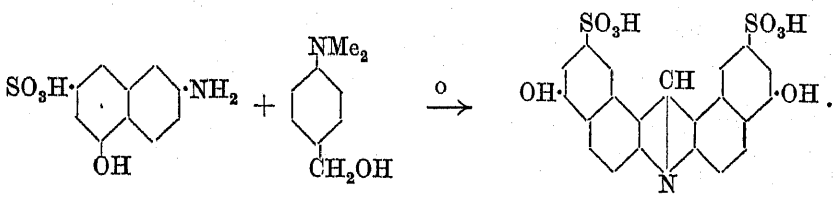


For the preparation of mixed phenonaphthacridines naphthols must be used in place of naphthylamines (see next section). A mixture of ψ-cumidine and β-naphthylamine, for example, gave only a mixture of hexamethylacridine and dinaphthacridine.[2]

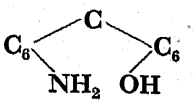
A number of more complex acridines have been synthesised by means of CH_2I_2 or CH_2Cl_2 from such compounds as 9-aminophenanthrene,[3] 2-aminofluorene,[4] and 6-aminoquinoline.[5]

[1] Senier and Austin, *J. C. S.*, 1908, **93**, 63. [2] *Idem, ibid.*, 1907, **91**, 1245.
[3] Austin, *ibid.*, 1908, **93**, 1764. [4] *Ibid.*, p. 1765. [5] Senier and Compton, *ibid.*, 1909, **95**, 1629.
* It is more convenient, however, to consider Senier's syntheses in this section. Moreover, the formation of di-β-naphthylamine does not necessarily imply that it is actually an intermediate stage in the reaction.

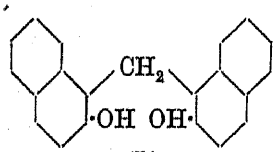
Certain aminonaphtholsulphonic acids (2 : 5 : 7, 2 : 6 : 8 and 1 : 5 : 7) give acridines by heating with a mixture of dimethylaniline and formaldehyde : [1]



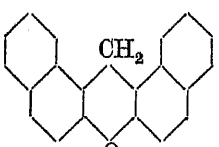
"*J-acid.*"

3. From β-naphthol, an aromatic amine and formaldehyde etc. : 

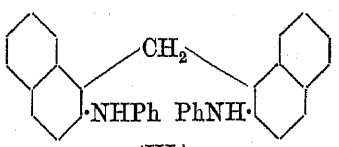
β-Naphthol condenses with formaldehyde to give methylene-di-β-naphthol (I). This compound was heated with aniline hydrochloride [2] in the hope of obtaining the corresponding *N*-phenyldihydrodinaphthacridine. The only products, however, were (II) and (III).



(I.)

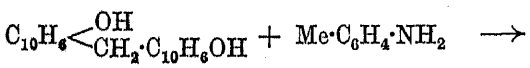


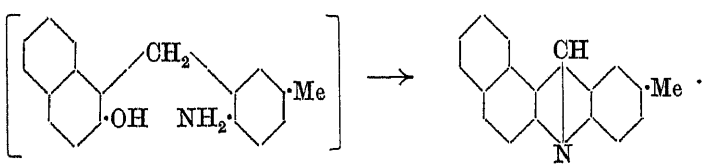
(II.)



(III.)

A quite different reaction results when *p*-toluidine is used instead of aniline. One equivalent of β-naphthol is displaced by the base, and the product is a phenonaphthacridine :





[1] D.R.-P. 272612.

[2] Ullmann and Naef, *Ber.*, 1900, **33**, 905.

The same compound results when the naphthol, aldehyde and toluidine are combined in different ways, *e.g.*

$$HCHO + \beta\text{-}C_{10}H_7OH + p\text{-}Me\cdot C_6H_4\cdot NH_2$$

or

$$CH_2{<}^{NH\cdot C_6H_4Me}_{NH\cdot C_6H_4Me} + \beta\text{-}C_{10}H_7\cdot OH$$

or

$$CH_2{:}N\cdot C_6H_4Me + \beta\text{-}C_{10}H_7\cdot OH.$$

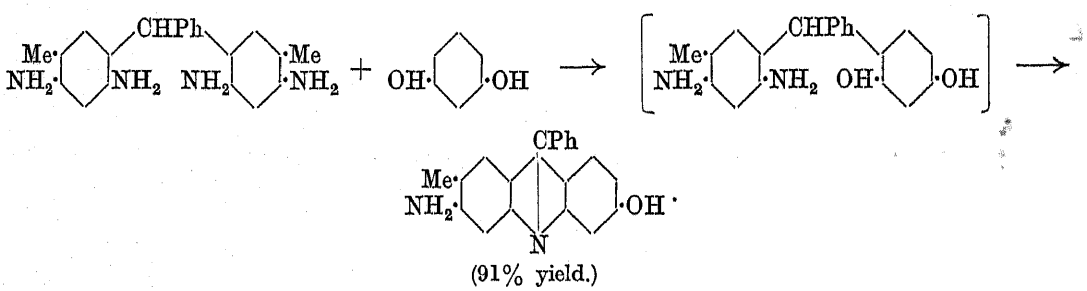
The reaction appears to be very general and has been applied to formaldehyde, benzaldehyde and *m*- and *p*-nitrobenzaldehyde * on the one hand, and *p*-toluidine, *o*-toluidine, *m*-xylidine, *p*-aminoacetanilide and *α*- and *β*-naphthylamines on the other.[1] In this way a large number of phenonaphthacridines and dinaphthacridines have been prepared.

m-Diamines react even more easily with methylene-di-*β*-naphthol than the simpler bases, and here again any combination of the three components may be employed.[2]

The yields vary considerably. Thus benzal-*p*-toluidine and *β*-naphthol give 39% of the corresponding acridine; from benzal-*m*-toluylenediamine the yield is 93·5%. *m*-Phenylenediamine gives only poor yields (24% from *β*-naphthol, trioxymethylene and the diamine; 18% from methylene-di-*β*-naphthol and the diamine; 10% from methylene-di-*m*-phenylenediamine and *β*-naphthol).

Zenoni [3] first observed the formation of a naphthacridine by the action of *β*-naphthol upon the condensation product from benzaldehyde and two molecular proportions of *m*-toluylenediamine. Ullmann employed various aromatic aldehydes and a large number of *m*-diamines.[4] The yields in the case of benzaldehyde are very good.

Ullmann and Fitzenkam [5] extended the reaction to *m*-aminophenols (*p*-amino-*o*-cresol, *β*-naphthol and benzaldehyde gave 88% yield, and the aminocresol methyl ether 85%). They also found that resorcinol could be used instead of *β*-naphthol with the methane base from *m*-toluylenediamine and benzaldehyde:



(91% yield.)

The substitution of CH_2Cl_2 or CH_2I_2 for formaldehyde gives good results both with *β*-naphthol

[1] D.R.-PP. 117472, 119573, 123260; Ullmann, Racovitza and Rozenband, *Ber.*, 1902, **35**, 316; Ullmann and Fetvadjian, *ibid.*, 1903, **36**, 1027.

[2] D.R.-PP. 104667, 104748, 130721, 130943; Ullmann and Naef, *ibid.*, 1900, **33**, 912; Ullmann and Maric, *ibid.*, 1901, **34**, 4317; Ullmann, Racovitza and Rozenband, *ibid*, 1902, **35**, 316; Ullmann and Bühler, *Zeitschr. Farb. Text. Ind.*, 1905, **4**, 521.

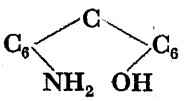
[3] D.R.-PP. 108273, 127586, 128754; Ullmann, Rozenband, Mühlhauser and Grether, *Ber.*, 1902, **35**, 326; Ullmann and Grether, *Zeitschr. Farb. Text. Ind.*, 1903, **2**, 89.

[4] *Gazz*, 1893, **23**, ii. 221.

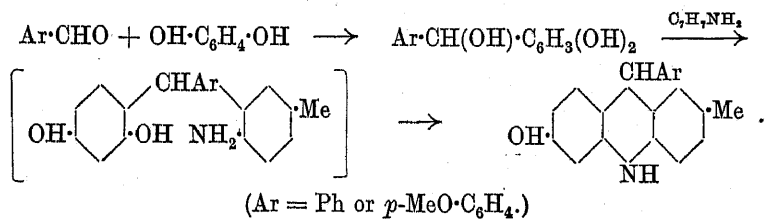
[5] *Ber.*, 1905, **38**, 3787.

* The yield is poor with *m*-nitrobenzaldehyde.

and with phenols.[1] The xylidines, naphthylamines, 2-aminofluorene and 6-aminoquinoline have been converted into naphthacridines in this way, and the xylidines have also been condensed with the corresponding xylenols to give tetramethylacridines.

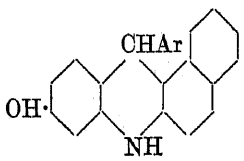
4. From o-amino-o'-hydroxybenzophenones etc.: 

The hydrols obtained by Pope and Howard[2] from resorcinol by condensation with benzaldehyde or *p*-anisaldehyde react with *p*-toluidine and *β*-naphthylamine (*i.e.* with *p*-substituted amines) to give dihydroacridines:

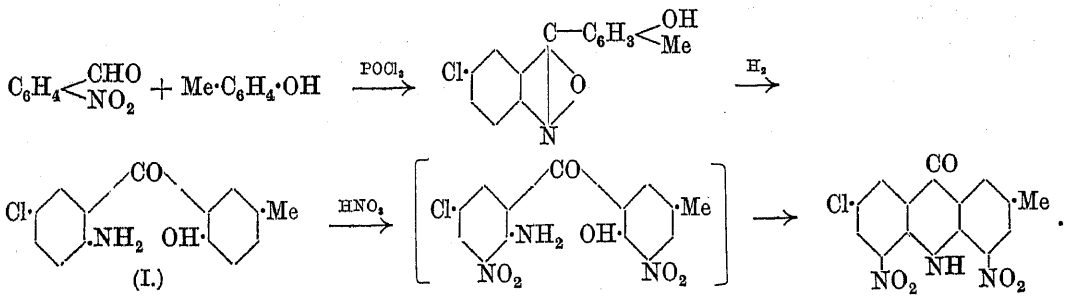


(Ar = Ph or *p*-MeO·C_6H_4.)

The *β*-naphthylamine products have the structure



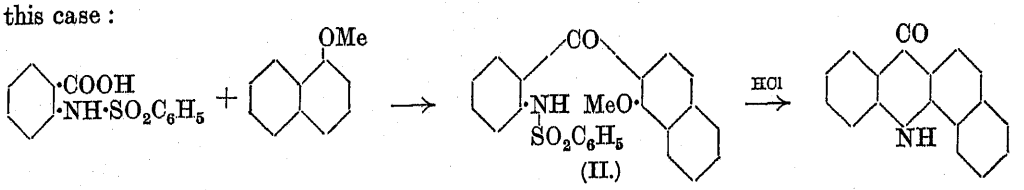
For the preparation of acridones (·CO in place of ·CHAr·) by a similar method the ·NH_2 group must be specially activated. Thus 2-amino-5-chloro-2'-hydroxy-5'-methylbenzophenone (I), obtained by Zincke and Siebert[3] by reduction of the anthroxan from *o*-nitrobenzaldehyde and *p*-cresol, only undergoes ring-closure after nitration:



(I.)

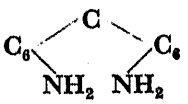
[1] Senier and Austin, *J. C. S.*, 1907, **91**, 1240; Senier and Compton, *ibid.*, p. 1931; 1909, **95**, 1623; Austin *ibid.*, p. 1766. [2] *Ibid.*, 1910, **97**, 83, 975. [3] *Ber.*, 1906, **39**, 1937.

Similarly Ullmann and Denzler[1] obtained phenonaphthacridine in 90% yield by the action of HCl at 150–180° upon the ketone (II). The benzenesulphonyl group is the activating agent in this case :

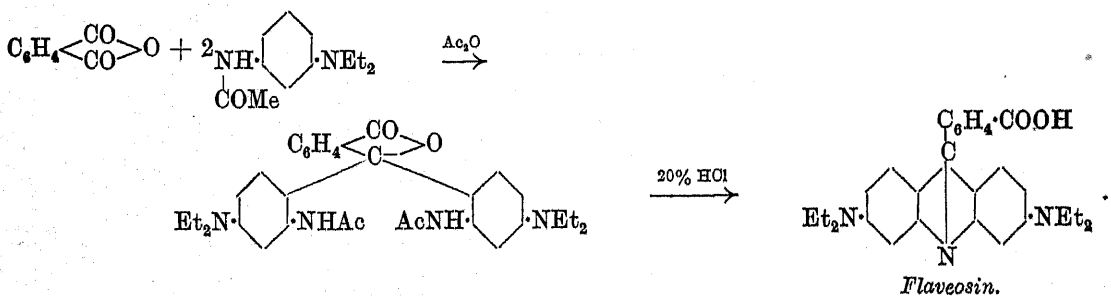


No activation is necessary in the naphthalene series for the preparation of dihydroacridines or acridines (see section 3 above).

5. From *m*-diamines etc. and phthalic anhydride etc. :



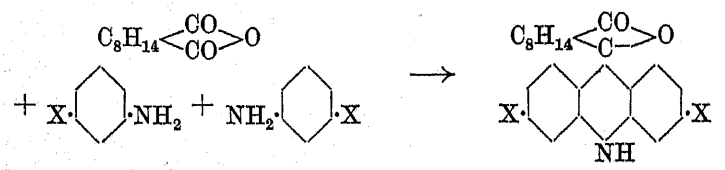
In the place of aldehydes phthalic anhydride (which shows many of the reactions of a ketone) may be condensed with *m*-diamines, and the products give acridines when treated with $ZnCl_2$ or 20% HCl. Thus from diethyl-*m*-aminoacetanilide and phthalic anhydride in the presence of acetic anhydride a phthalein is obtained which is converted by H_2SO_4 or HCl into Flaveosin.[2] The constitution of this dyestuff was finally elucidated by Grandmougin and Lang : [3]



Flaveosin.

A similar dyestuff is prepared from phthalic anhydride and *m*-phenylene- or *m*-toluylene-diamine with zinc chloride.[4]

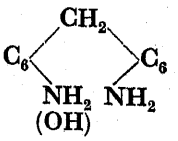
Sircar and Dutt[5] have condensed *m*-phenylenediamine and also *m*-aminophenol with camphoric anhydride and have isolated the corresponding dihydroacridine derivatives :



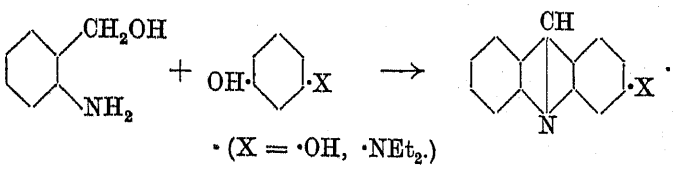
(X = ·OH or ·NH_2.)

[1] *Ber.*, 1906, **39**, 4339.
[2] D.R.-P. 49850.
[3] *Ber.*, 1909, **42**, 4014.
[4] D.R.-P. 141356.
[5] *J. C. S.*, 1922, **121**, 1286.

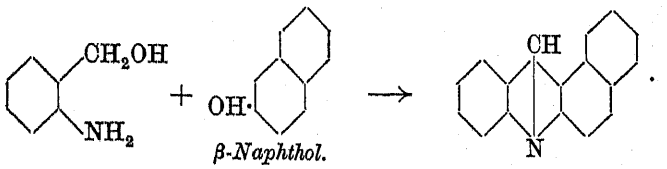
6. From *o*-nitrobenzyl chloride etc.:



Ullmann and Baezner [1] obtained acridines by condensing *o*-aminobenzyl alcohol with β-naphthol, resorcinol or diethyl-*m*-aminophenol:

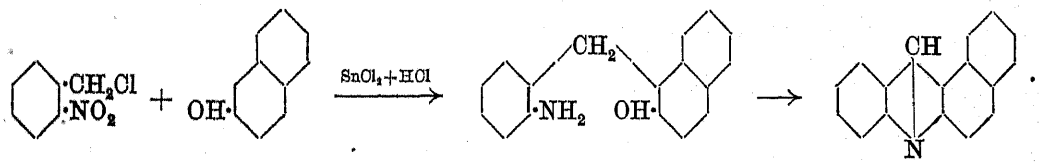


·(X = ·OH, ·NEt$_2$·)

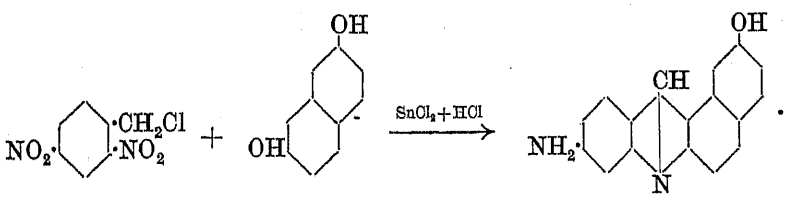


β-Naphthol.

The reaction was developed by Baezner,[2] who found that a mixture of *o*-nitrobenzyl chloride and β-naphthol gave phenonaphthacridine by treatment with $SnCl_2$ and HCl:



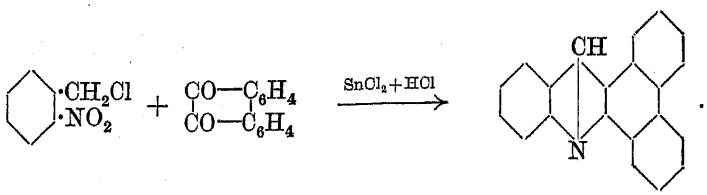
β-Naphthylamine and phenyl-β-naphthylamine give the same result, NH_3 and $PhNH_2$ respectively being eliminated. 2 : 6- and 2 : 7-Dihydroxynaphthalenes yield a hydroxy derivative, but the reaction fails with 2 : 3-dihydroxynaphthalene. 2 : 4-Dinitrobenzyl chloride reacts more readily than the mono-nitro compound, the products being aminoacridines: [3]



2 : 3-Dihydroxynaphthalene mono-methyl ether, which does not condense with *o*-nitrobenzyl chloride, gives good yields with the dinitro compound.

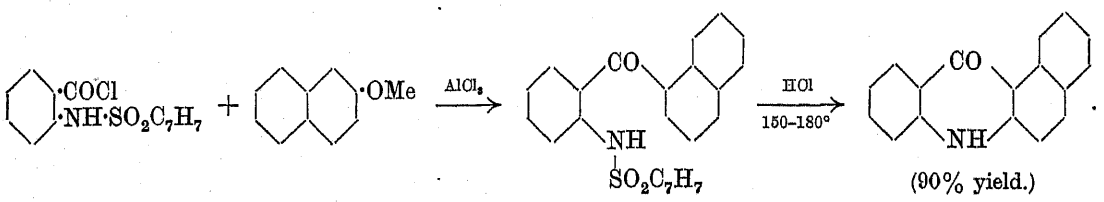
[1] *Ber.*, 1902, **35**, 2670. [2] *Ibid.*, 1904, **37**, 3077.
[3] Baezner and Gueorguieff, *ibid.*, 1906, **39**, 2438.

Austin [1] used Baezner's method for the synthesis of a phenanthacridine from phenanthraquinone:



A modification of the reaction consists in condensing *o*-nitrobenzyl chloride first with aniline and reducing the product to *o*-aminobenzylaniline. This substance gives a naphthacridine when heated with *β*-naphthol or 2 : 7-dihydroxynaphthalene in the presence of HCl, aniline being eliminated.[2]

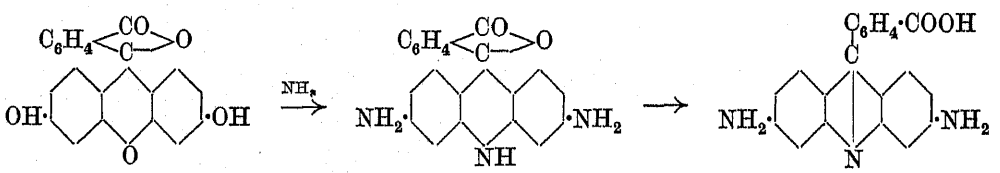
A related synthesis is that of phenonaphthacridone by Ullmann and Denzler: [3]



7. From fluorescein etc.: $C_6<\overset{C}{\underset{O}{>}}C_6$

m-Hydroxy-xanthones form an exception to the general rule that an oxygen ring compound is only convertible by NH_3 into the corresponding nitrogen ring compound when the oxygen linkages are both aliphatic. The replacement in the case of these xanthones seems to be due to the same cause which enables resorcinol to be "amidated" comparatively easily, and is probably connected with the capacity for the assumption of a quinonoid configuration.

Fluorescein by the action of ammonia under pressure gives a diaminoacridine [4]:

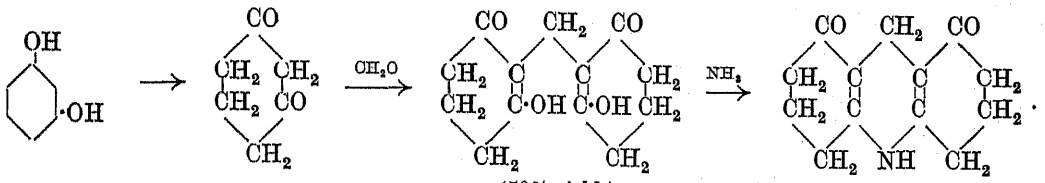


Fluorescein.

A somewhat similar synthesis of a decahydroacridine derivative was devised by Vorländer.[5]

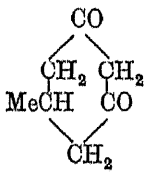
[1] *J. C. S.*, 1908, **93**, 1765. [2] Baezner and Gardiol, *Ber.*, 1906, **39**, 2623. [3] *Ibid.*, p. 4332.
[4] D.R.-PP. 73334, 75933; R. Meyer, *Ber.*, 1888, **21**, 3376; 1891, **24**, 1413; 1899, **32**, 2352.
[5] *Ibid.*, 1897, **30**, 1803; *Ann.*, 1899, **309**, 356, 375, 380.

Resorcinol was reduced by sodium amalgam to dihydroresorcinol, which was condensed with formaldehyde and then treated with alcoholic ammonia :

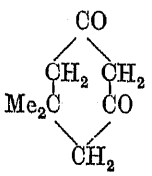


(50% yield.) (65% yield.)

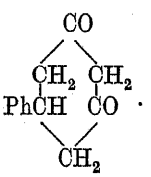
Hydrogenated diketoacridines were also obtained from the condensation products of dihydroresorcinol with benzaldehyde, dihydro-orcinol with formaldehyde, 5 : 5-dimethyldihydroresorcinol with benzaldehyde and cuminaldehyde, and 5-phenyldihydroresorcinol with benzaldehyde.



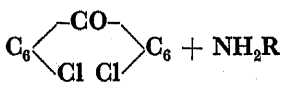
Dihydro-orcinol.



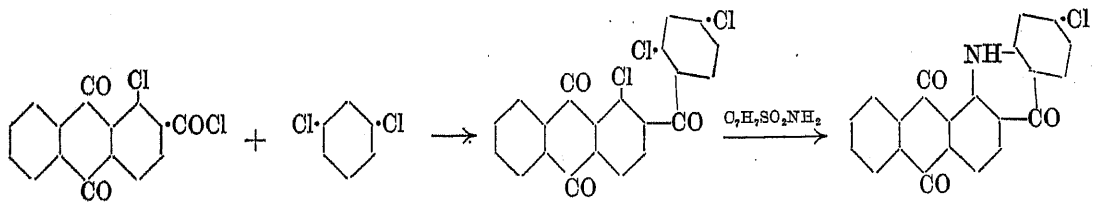
5 : 5-*Dimethyldihydroresorcinol.*



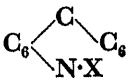
5-*Phenyldihydroresorcinol.*

8. From *o* : *o'*-dichlorobenzophenones : 

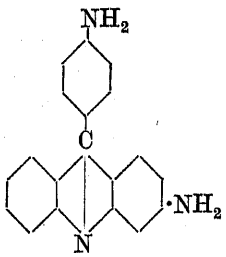
From 1-chloroanthraquinone-2-carboxylic chloride and *m*-dichlorobenzene by Friedel-Crafts' reaction a trichlorobenzoylanthraquinone is obtained, which reacts with *p*-toluenesulphonamide in the presence of sodium acetate and Cu to give a chloroanthracridone, the sulphonyl group being eliminated during the condensation [1] :



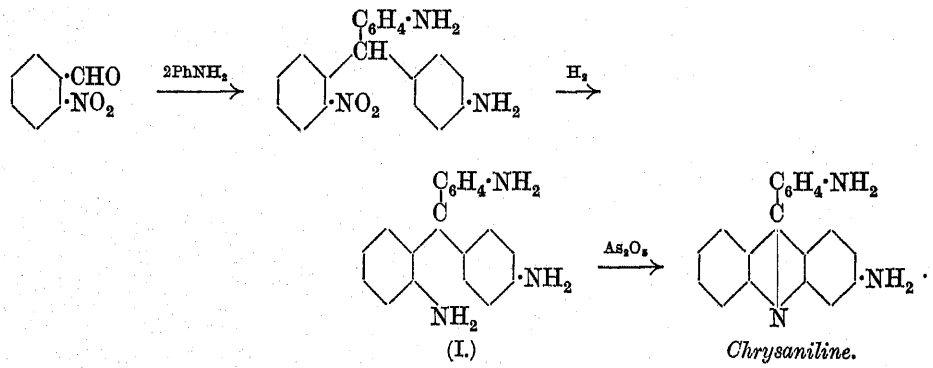
[1] D.R.-P. 272297.

9. By oxidation of *o*-amino-diphenylmethanes or reduction of *o*-nitrodiphenylmethanes : 

In the preparation of Magenta by the oxidation of a mixture of aniline and *o*- and *p*-toluidines with As_2O_5 or $HgSO_4$ there is always formed as a by-product a yellow acridine dyestuff, Chrysaniline, which appears in commerce as impure nitrate or hydrochloride under the name of "Phosphine." Pure Chrysaniline may be obtained from the commercial product in about 50% yield [1] and has been carefully investigated by Hofmann [2] and by O. Fischer and Körner.[3] The latter authors showed that Chrysaniline had the constitution :



and obtained it synthetically by oxidation of Renouf's triaminotriphenylmethane (I) [4] with As_2O_5 at 150–180° :



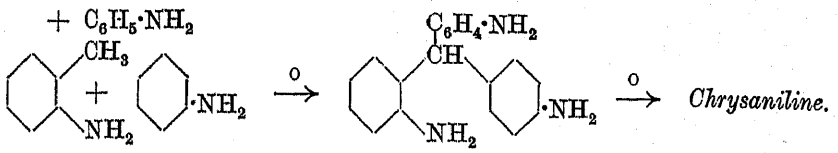
(I.)

Chrysaniline.

In a similar manner, from *o*-nitrobenzaldehyde and dimethylaniline, Fischer and Körner obtained tetramethylchrysaniline. In this case, the yield is increased to 40% by substituting yellow HgO for As_2O_5 in the final oxidation.[5]

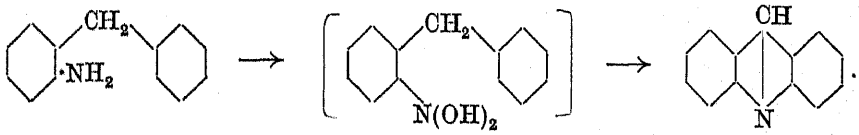
[1] Fischer and Körner, *Ann.*, 1884, **226**, 175.
[2] *Ber.*, 1869, **2**, 379.
[3] *Loc. cit.* and *Ber.*, 1884, **17**, 203.
[4] *Ibid.*, 1883, **16**, 1304.
[5] O. Fischer and Schätte, *ibid.*, 1893, **26**, 3085.

The formation of Chrysaniline in the Magenta process * is explained on the lines of Fischer and Körner's synthesis :

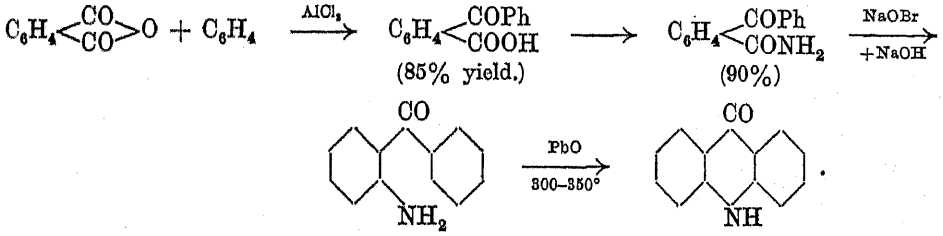


The preparation of substituted chrysanilines by oxidation of various mixtures of bases is claimed in D.R.-PP. 65985, 78377, 79263, 79585, 79877, 81048 and 122854.

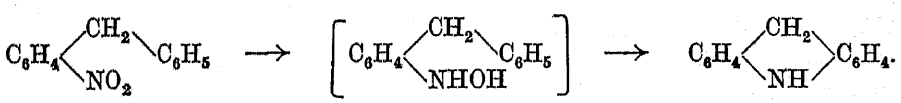
O. Fischer and Schütte [1] synthesised acridine itself by oxidation of *o*-aminodiphenylmethane with lead oxide :



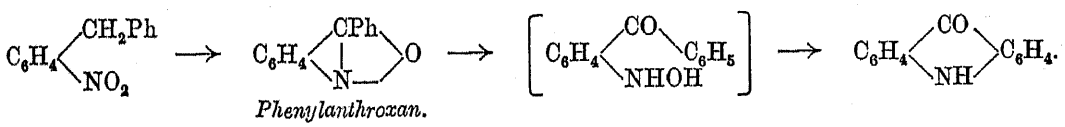
Acridone is obtained in 40–50% yield by a similar oxidation of *o*-aminobenzophenone [2] :



The hydroxylated nitrogen compound which may be regarded as an intermediate in these syntheses is also obtainable by reduction of *o*-nitrodiphenylmethane derivatives. Thus O. Fischer [3] prepared dihydroacridine in this way :



The conversion of anthroxan derivatives into acridines is closely related to the Fischer synthesis. By the action of heat upon *o*-nitrodiphenylmethane Kliegl [4] obtained acridone in 35–38% yield, phenylanthroxan being an isolable intermediate :

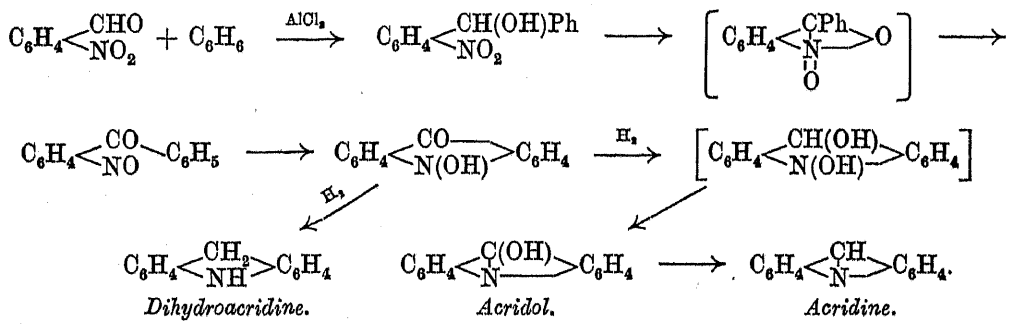


[1] *Ber.*, 1893, **26**, 3085.
[2] Graebe and Ullmann, *Ann.*, 1896, **291**, 15.
[3] *Ber.*, 1895, **28**, 1335.
[4] *Ibid.*, 1909, **42**, 591.

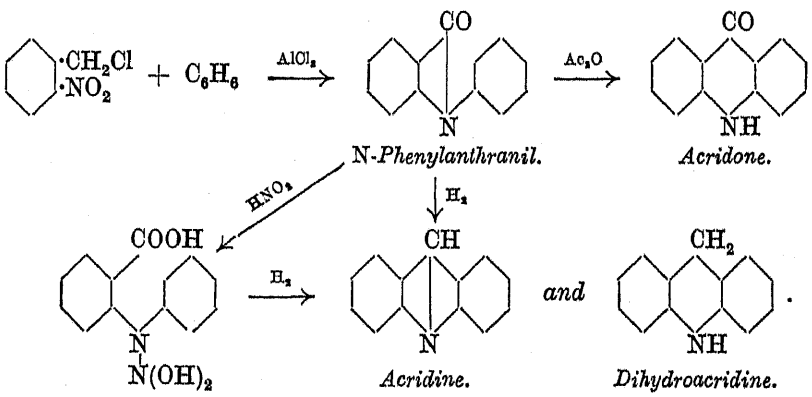
* The suggestion that aminodiphenylamine (from the aniline) condenses with *p*-aminobenzoic acid (from the *p*-toluidine), as in the Bernthsen synthesis, does not fit the facts, for this would give a chrysaniline in which the acridine amino group was *para* to the N instead of to the C atom.

Phenyl- and *p*-tolyl-anthroxans are converted into acridone and 3-methylacridone by treatment with sodium nitrite and HCl.[1]

In the preparation of phenylanthroxan from *o*-nitrobenzaldehyde, benzene and conc. H_2SO_4 or $AlCl_3$, Kliegl [2] obtained as a by-product *N*-hydroxyacridone which on reduction gives acridol, acridine and dihydroacridine :



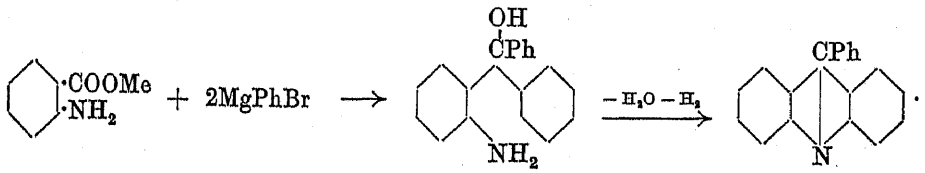
A small amount of acridine appears amongst the products of the interaction of *o*-nitrobenzyl chloride, benzene and $AlCl_3$, the main product being *o*-nitro-diphenylmethane.[3] Drechsler [4] isolated *N*-phenylanthranil from the reaction products and showed that it gave acridone by the action of acetic anhydride and acridine on reduction :



[1] Bamberger, *Ber.*, 1909, **42**, 1716.
[2] *Chem. Zeitung*, 1907, **31**, 330; 1913, **37**, 1006; *Ber.*, 1914, **47**, 1629.
[3] Koenigs and Nef, *ibid.*, 1886, **19**, 2431; O. Fischer, *ibid.*, 1895, **28**, 1335; Freund, *Monatsh.*, 1896, **17**, 395.
[4] *Ibid.*, 1914, **35**, 533.

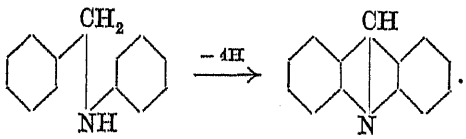
10. From anthranilic ester and magnesium phenyl bromide : $C_6<\begin{matrix}C(OH)\\NH_2\end{matrix}>C_6$

The triarylcarbinol obtained by the action of excess of PhMgBr upon methyl anthranilate is converted into 5-phenylacridine when heated. The conversion is best with the picrate, which requires a temperature of only 100° [1]:

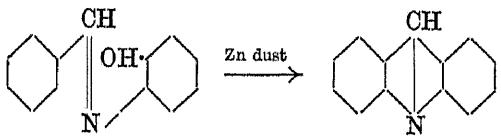


11. From benzyl- or benzal-aniline etc. : $C_6<\begin{matrix}C\\|\\N\end{matrix}>C_6$

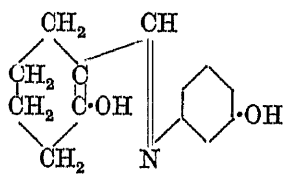
When benzylaniline is passed through a hot tube considerable quantities of acridine are formed.[2] No phenanthridine or benzanilide is found in the reaction product, and indeed this method is a very convenient one for the preparation of acridine :



Under the same conditions benzalaniline gave no nitrogen ring compound but only aniline, benzonitrile, benzene and diphenyl. Reddelien, however,[3] obtained a little acridine by heating benzalaniline with a trace of aniline hydrobromide at 230–290°. Acridine is also formed when benzal-*o*-aminophenol is distilled with zinc dust [4]:

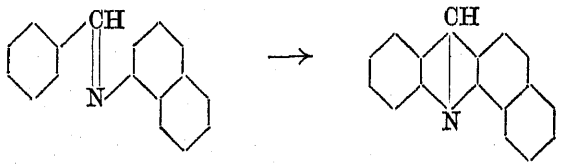


but not by the dehydration of the somewhat similarly constituted hydrogenated compound (I) [5]:

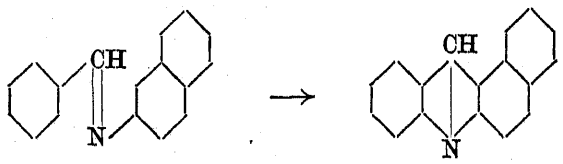


[1] v. Baeyer and Villiger, *Ber.*, 1904, **37**, 3200. [2] Meyer and Hofmann, *Monatsh.*, 1916, **37**, 681–722.
[3] *Ber.*, 1920, **53**, 356. [4] Pictet and Ankersmit, *ibid.*, 1889, **22**, 3339; *Ann.*, 1891, **266**, 138.
[5] Borsche, *ibid.*, 1910, **377**, 87.

α- and β-Chrysidines, prepared by Pictet and Erlich [1] from benzal-α- and -β-naphthylamines and supposed by them to be phenanthridines, were shown by Ullmann and La Torre [2] to be α- and β-naphthacridines :

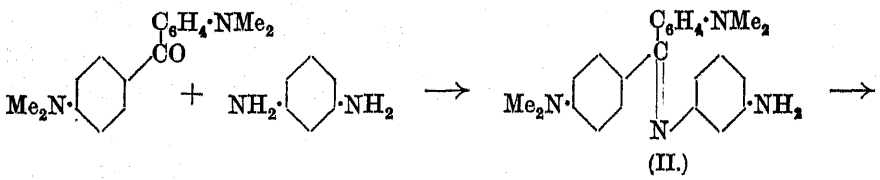


α-Chrysidine.

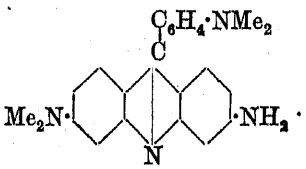


β-Chrysidine.

In the preparation of Rheonine from Michler's ketone (or hydrol), *m*-phenylenediamine and zinc chloride at 200°,[3] the first product is a *m*-aminophenylauramine (II), which is converted into the acridine derivative by loss of hydrogen [4] :

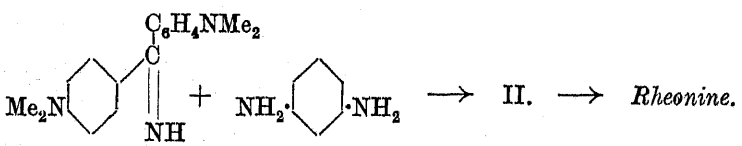


(II.)



Rheonine.

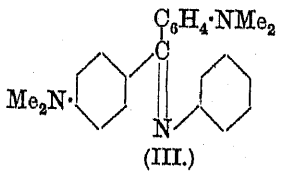
This view of the reaction is confirmed by the production of Rheonine by heating with $ZnCl_2$ the condensation product from Auramine base and *m*-phenylenediamine :

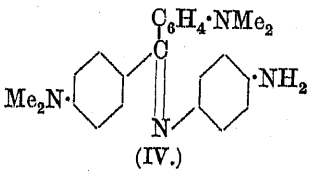


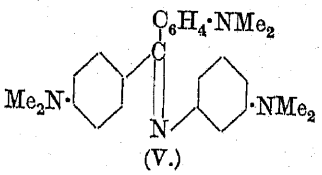
Auramine base.

[1] *Ann.*, 1891, **266**, 153.
[2] *Ber.*, 1904, **37**, 2922; see also Graebe, *Ann.*, 1904, **311**, 124.
[3] D.R.-PP. 82989, 85199.
[4] Grandmougin and Lang, *Ber.*, 1909, **42**, 3631.

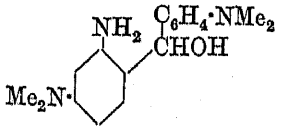
No acridines were obtained from phenyl-auramine (III) and *p*-aminophenyl-auramine (IV); but dimethyl-*m*-aminophenyl-auramine (V)

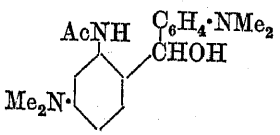

(III.)


(IV.)

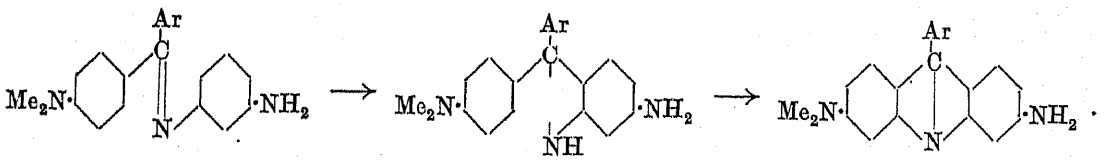

(V.)

yields dimethyl-Rheonine. Rheonines are also obtained from diaminobenzophenone [1] and by condensation of the *o*-amino- (VI) or *o*-acetamino- (VII) derivative of Michler's hydrol with *m*-diamines or *para*-substituted amines such as *p*-toluidine and *β*-naphthylamine.[2] Alternatively, the methane base from dimethylaniline or *o*-toluidine may be condensed in the presence of AmCl with the thio-bases obtained by the action of sulphur upon *m*-tolylenediamine, *m*-aminodimethylaniline and 2 : 4-diaminoanisole.[3]

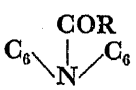

(VI.)


(VII.)

Acridine formation is apparently facilitated by the presence of an activating group *meta* to the N, *i.e. para* to the new linkage with the *meso* carbon atom. On the other hand, this may be due to the (*para*) directing power of the "activating" group, ring-closure being preceded by migration in some such manner as the following:



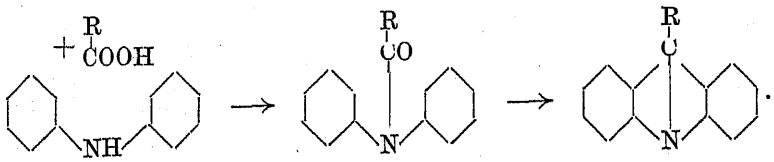
This would account for the formation of acridines from *p*-toluidine and *β*-naphthylamine in which migration to the *para* position is inhibited.

12. From diphenylamines and acids: 

This very generally applicable method dates from 1878, when Bernthsen [4] heated diphenylamine hydrochloride and benzonitrile at 230–250° and obtained in 10% yield a base, $C_{19}H_{13}N$, which was later shown to be 5-phenylacridine.[5] The same product is obtained much more smoothly by heating benzoyldiphenylamine or a mixture of benzoic acid and diphenylamine with $ZnCl_2$.[6]

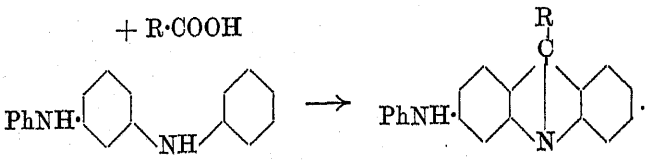
[1] D.R.-P. 89660. [2] D.R.-PP. 114261, 116353. [3] D.R.-P. 288841.
[4] *Ann.*, 1878, **192**, 19. [5] Bernthsen, *Ber.*, 1882, **15**, 3011; Bernthsen and Bender, *ibid.*, 1883, **16**, 1802.
[6] Bernthsen, *ibid.*, p. 767.

Besthorn and O. Fischer [1] prepared a base, $C_{14}H_{11}N$, from diphenylamine, acetic acid and $ZnCl_2$, and the identification of this product as 5-methylacridine [2] led to a generalisation of Bernthsen's method and its extension to a large number of acylated diphenylamines :



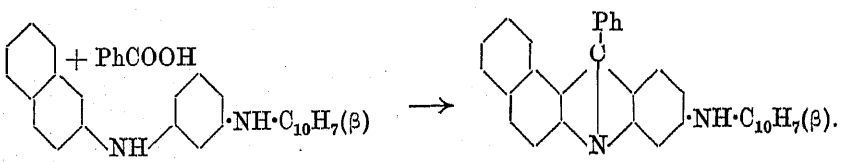
Acridine itself is obtained in only small yield by using formic or oxalic acid,[3] but chloroform, especially in the presence of $AlCl_3$, gives satisfactory results.[4] The yields with other acids, aromatic or aliphatic, are from 40–60%. The reaction fails with *p*-nitrobenzoic acid and with cinnamic acid.

Substituted diphenylamines give the corresponding acridines, *e.g.* : [5]

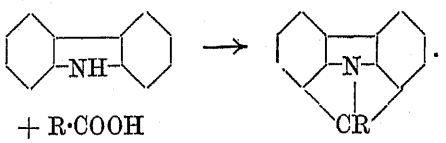


(R = H, Me, Ph, *o*-COOH·C_6H_4.)

O. Fischer and Schütte [6] prepared a phenonaphthacridine from di-β-naphthyl-*m*-phenylenediamine and benzoic acid :



Bizzarri [7] claimed to have converted carbazole into " carbazacridines " by heating it with benzoic or acetic acid and $ZnCl_2$ or with benzamide or acetamide and P_2O_5. His results have not been confirmed. The reaction is stated to be :



[1] *Ber.*, 1883, **16**, 74. [2] Bernthsen and Bender, *loc. cit.*; O. Fischer, *Ber.*, 1883, **16**, 1820.
[3] Bernthsen, *Ann.*, 1884, **224**, 3, 6. [4] Fischer and Körner, *Ber.*, 1884, **17**, 101.
[5] Besthorn and Curtmann, *ibid.*, 1891, **24**, 2042. [6] *Ibid.*, 1893, **26**, 3086.
[7] *Gazz.*, 1890, **20**, 407; 1891, **21**, ii. 158, 351; 1893, **23**, i. 1.

The following diphenylamines and acids have been used in the preparation of acridines by Bernthsen's method:

(a) *From diphenylamine:*

Acid.	*References.*
Formic	9
Oxalic	9
(Chloroform)	7
Acetic	3, 6, 9
Propionic	16
Butyric	16
Valeric	8, 9
Palmitic	16
Stearic	17
Succinic	17
Phenylacetic	21
Benzoic	4, 9, 19, 24
(Benzonitrile)	1, 2, 5
o-, *m*-, and *p*-Toluic	23
2 : 4-Dimethylbenzoic	23
3 : 5-Dimethylbenzoic	23
o- and *m*-Nitrobenzoic	11
o-, *m*-, and *p*-Hydroxybenzoic	22
p-Chlorobenzoic	26
p-Bromobenzoic	25
p-Aminobenzoic	11
Phthalic	8, 9, 11, 20, 21

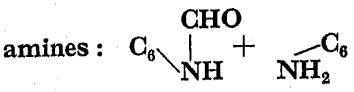
(b) *From substituted diphenylamines:*

Diphenylamine.	*Acid.*	*References.*
Phenyl-*p*-tolylamine	Formic	13
	Acetic	13
	Benzoic	13
4-Hydroxydiphenylamine	Benzoic	28
4-Aminodiphenylamine	Benzoic	27
symm-Diphenyl-*m*-phenylenediamine	Formic	15
	Acetic	15
	Benzoic	15
	Phthalic	15
symm-Di-β-naphthyl-*m*-phenylenediamine	Benzoic	18
Carbazole	Acetic	14
	Benzoic	14

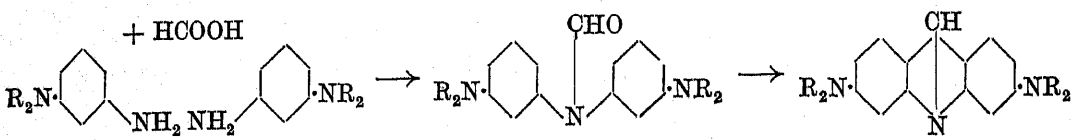
References.

[1] Bernthsen, *Ann.*, 1878, **192**, 19. [2] *Idem*, *Ber.*, 1882, **15**, 3011. [3] Besthorn and O. Fischer, *ibid.*, 1883, **16**, 74. [4] Bernthsen, *ibid.*, p. 767. [5] Bernthsen and Bender, *ibid.*, p. 1802. [6] Fischer, *ibid.*, p. 1820. [7] Fischer and Körner, *ibid.*, 1884, **17**, 101. [8] Bernthsen and Traube, *ibid.*, p. 1508. [9] Bernthsen, *Ann.*, 1884, **224**, 3, 6, 13, 34, 41, 45. [10] D.R.-P. 29142. [11] Bernthsen and Hess, *Ber.*, 1885, **18**, 689. [12] Bernthsen, *ibid.*, 1887, **20**, 1552. [13] Bonna, *Ann.*, 1887, **239**, 63. [14] Bizzarri, *Gazz.*, 1890, **20**, 407; 1891, **21**, ii. 158, 351; 1893, **23**, i. 1. [15] Besthorn and Curtmann, *Ber.*, 1891, **24**, 2042. [16] Volpi, *Gazz.*, 1891, **21**, ii. 228. [17] *Idem*, *R. A. L.*, 1892, v. **1**, ii. 132. [18] Fischer and Schütte, *Ber.*, 1893, **26**, 3086. [19] Claus and Beckenkamp, *J. pr. Chem.* 1893, **48**, 222. [20] Dammann and Gattermann, *Z. Farb. Text. Chem.*, 1902, **1**, 325. [21] Decker and Hock, *Ber.*, 1904, **37**, 1006, 1565. [22] Landauer, *Bull.*, 1904, iii. **31**, 1083. [23] Schmidt and Decker, *Ber.*, 1906, **39**, 933. [24] Dunstan and Oakley, *ibid.*, p. 977. [25] Dunstan and Stubbs, *ibid.*, p. 2402. [26] Dunstan and Hilditch, *J. C. S.*, 1907, **91**, 1659. [27] Kehrmann, *Ber.*, 1908, **41**, 4135. [28] *Idem*, *ibid.*, 1912, **45**, 3499.

13. From formanilide etc. and *m*-diamines or *p*-substituted amines:



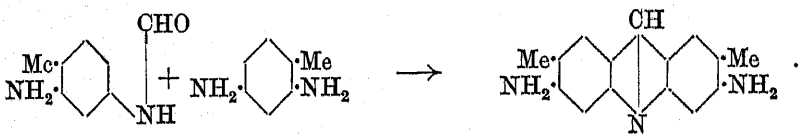
This is a modification of Bernthsen's synthesis, in which the formyl derivative of a *para*-substituted arylamine (or of a *meta*-diamine) is heated with the hydrochloride of a similar arylamine or *meta*-diamine. The earliest reaction of this type is the preparation of acridine dyestuffs by heating *m*-diamines with formic acid and $ZnCl_2$ [1]:



(R = Me, Et.)

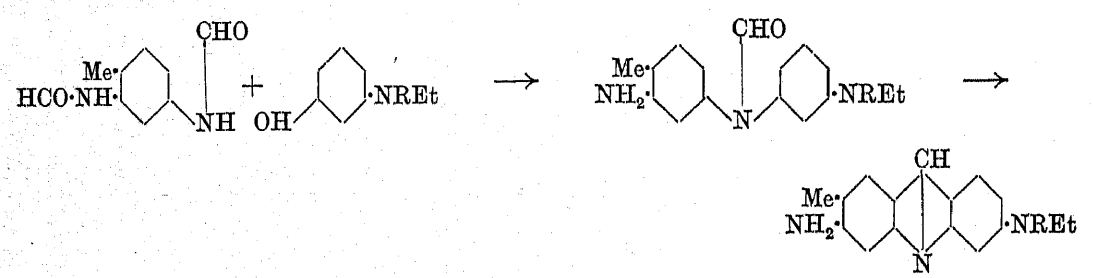
m-Amino derivatives of ethylaniline, methyl-*o*-toluidine or ethyl-*o*-toluidine may also be used.

The yellow dyestuffs of D.R.-P. 149409, formed by heating formyl-*m*-tolylenediamine alone or with *m*-diamines, are probably of the same type *:



Acridine yellow.

Ethylamino- and diethylamino-phenols have been condensed with diformyl-*m*-tolylenediamine,[2] and the production of acridines in this way is confirmation of the view that the reaction proceeds *via* the formyldiphenylamine derivative:



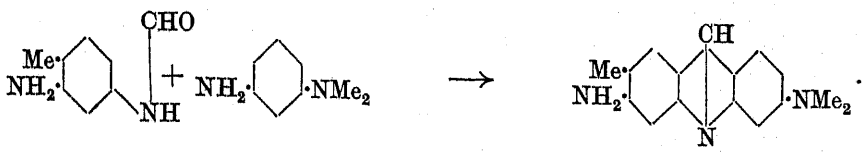
(R = H, Et.)

In a number of recent German patents [3] this reaction is extended and modified as indicated

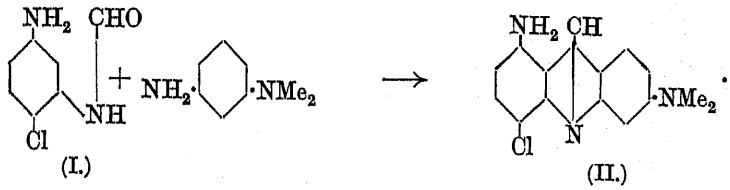
[1] D.R.-P. 67126. [2] D.R.-P. 161699. [3] D.R.-PP. 292848, 307165, 346961–346963.

* Undue weight must not be attached to the statement in the patent that the product from formyl-*m*-tolylenediamine is different from Acridine Yellow.

above. For example, *m*-aminodimethylaniline reacts with formyl-*m*-tolylenediamine to give 2-amino-8-dimethylamino-3-methylacridine :

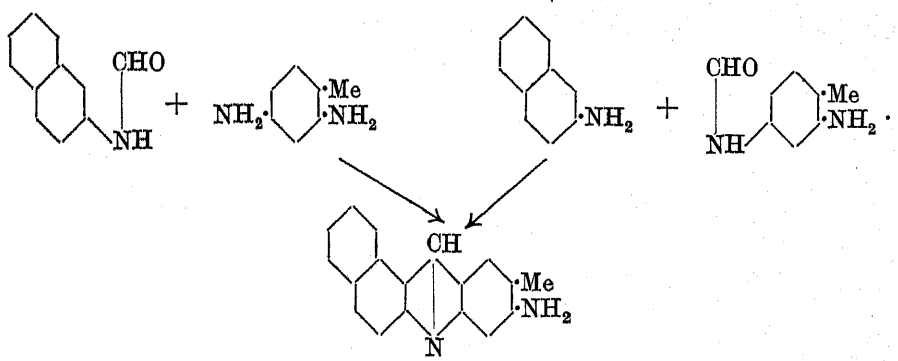


3-Amino-6-chloroformanilide (I) similarly yields the acridine (II) :

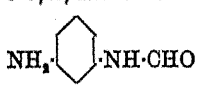


(I.) (II.)

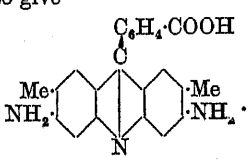
A phenonaphthacridine may be obtained either from *m*-tolylenediamine and formyl-*β*-naphthylamine or from formyl-*m*-tolylenediamine and *β*-naphthylamine :



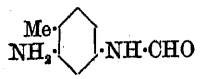
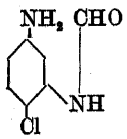
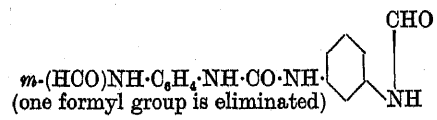
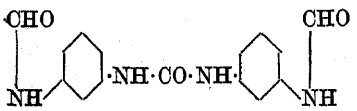
The following condensations of formyl derivatives with amines* are described in the patent literature :

Formyl derivative.	*Amine.*	*References.*
Ph·NH·CHO	*m*-Tolylenediamine.	3
o-C_7H_7·NH·CHO	*m*-Phenylenediamine.	3
	*m*-Tolylenediamine.	2
	Ethyl-*m*-tolylenediamine.	5
	β-Naphthylamine.	8
	m : *m*-Diaminodiphenylurea.	6

* As a further extension of the reaction may be regarded the condensation of phthalyl-*m*-tolylenediamine with *m*-tolylenediamine (D.R.-P. 141356) to give

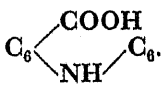


(See sect. 5.)

Formyl derivative.	*Amine.*	*References.*
	Aniline.	2
	p-Toluidine.	2
	m-Aminoethylaniline.	1
	m-Aminodimethylaniline.	4, 5
	m-Tolylenediamine.	2, 1, 7
	Methyl-*m*-tolylenediamine.	1, 5
	Ethyl-*m*-tolylenediamine.	1, 7, 4
	Dimethyl-*m*-tolylenediamine.	5
	β-Naphthylamine.	2
	Ethyl-*m*-aminophenol.	4
	Diethyl-*m*-aminophenol.	4
	m : *m*-Diaminodiphenylurea.	2
	*m*-Aminodimethylaniline.	5
β-$C_{10}H_7$·NH·CHO	*m*-Tolylenediamine.	9
	m-Aminodimethylaniline.	9
	p-Amino-methyl-*o*-toluidine.	9
 (one formyl group is eliminated)	*m*-Tolylenediamine.	6
	m-Aminodimethylaniline.	6
	β-Naphthylamine.	6
	2 mols. *m*-Aminodimethylaniline.	6
	m : *m*-Diaminodiphenylurea.*	6

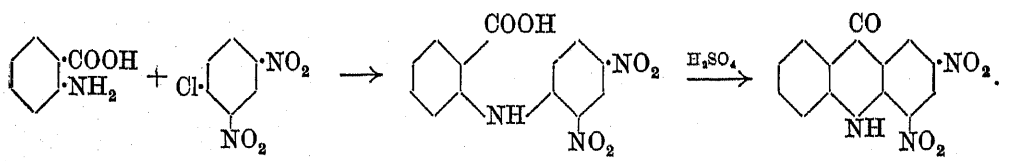
References.

[1] D.R.-P. 67126. [2] D.R.-P. 149409. [3] D.R.-P. 149410. [4] D.R.-P. 161699. [5] D.R.-P. 292848.
[6] D.R.-P. 307165. [7] D.R.-P. 346961. [8] D.R.-P. 346962. [9] D.R.-P. 346963.

14. From aryl-o-amino-acids: 

(a) *Acridones of the benzene series:*

This method was first used by Jourdan,[1] who condensed anthranilic acid with 2 : 4-dinitrochlorobenzene and heated the product with conc. H_2SO_4:

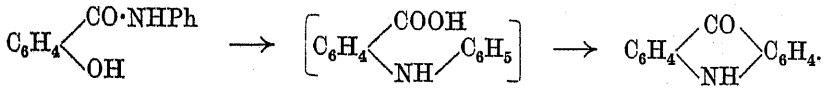


(I.)

* This condensation gives two mols. of diaminoacridine, both the urea carbonyls being lost.

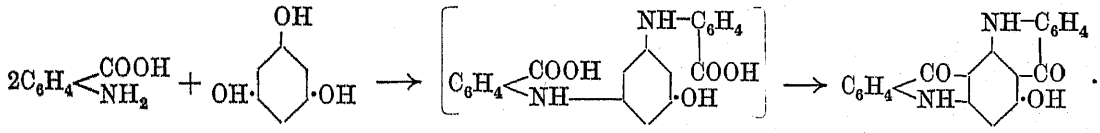
[1] *Ber.*, 1885, **18**, 1444.

The ring-closure occurs readily in most cases, the chief difficulty originally being the preparation of arylanthranilic acids of the type (I). Salicylanilide when strongly heated isomerises to phenylanthranilic acid, which then loses water and forms acridone [1]:

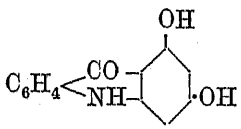


The *o*- and *p*-toluidides behave similarly.

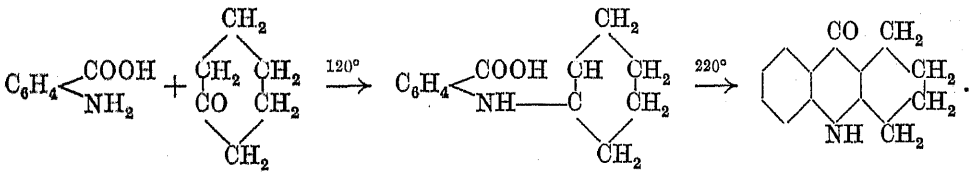
Phloroglucinol condenses with two molecular proportions of anthranilic acid to give a "quinacridine" [2]:



A certain amount of the dihydroxyacridone

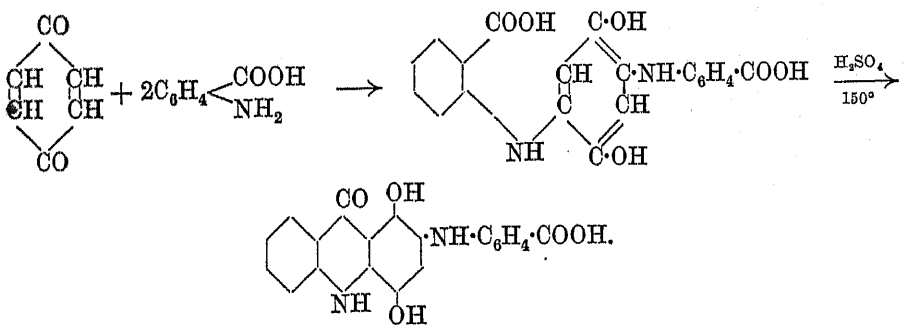


is also formed. From *cyclo*hexanone and anthranilic acid Borsche and Tiedtke [3] obtained tetrahydroacridone:



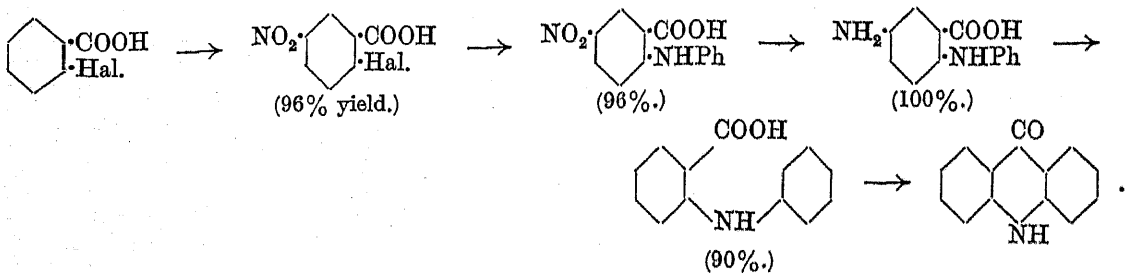
The product yielded acridone by air oxidation at 280° or acridine by distillation with zinc dust.

Benzoquinone forms a dicarboxydianilide with anthranilic acid, but only a single acridonation can be brought about with conc. H_2SO_4: [4]

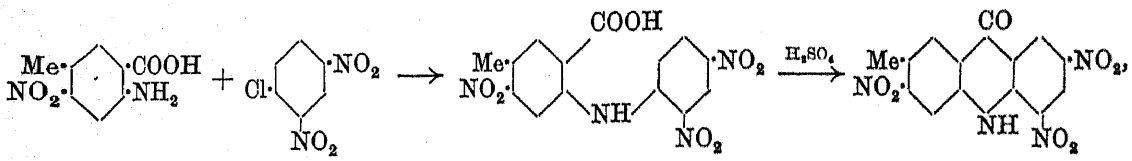


[1] Pictet and Hubert, *Arch. Sciences phys. nat.*, 1893, 215; *Ber.*, 1896, **29**, 1189.
[2] v. Niementowski, *ibid.*, p. 76; Baczyński and v. Niementowski, *ibid.*, 1905, **38**, 3009; 1919, **52**, 461.
[3] *Ibid.*, 1908, **41**, 2203; 1909, **42**, 624.
[4] Suchanek, *J. pr. Chem.*, 1914, **90**, 475, 486.

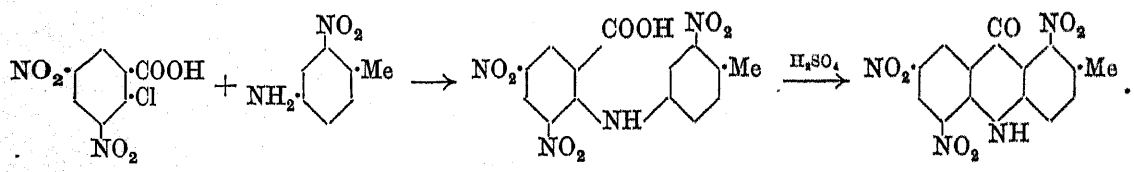
The introduction of a nitro-group activates the halogen in *o*-chloro- and *o*-bromo-benzoic acids so that it becomes easily replaceable by an arylamino group. Thus Graebe and Lagodzinski [1] prepared acridone by the following series of reactions :



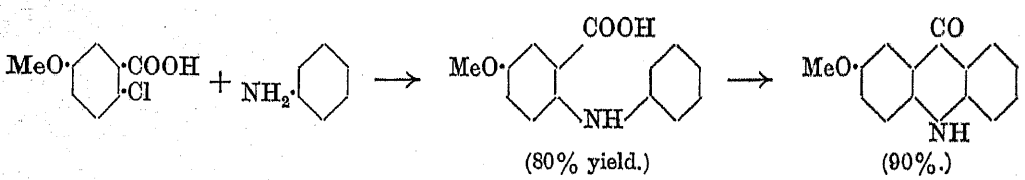
The use of dinitrochlorobenzene with anthranilic acid (Jourdan) has already been mentioned. Two trinitro-methylacridones have been prepared—the first from dinitrochlorobenzene [2] :



the second from 3 : 5-dinitro-*o*-chlorobenzoic acid [3] :



These tedious methods were no longer necessary when it was discovered that arylanthranilic acids could be obtained in almost quantitative yields from arylamines and *o*-chlorobenzoic acids, or from anthranilic acids and aryl halides, both reactions occurring readily in the presence of copper powder and K_2CO_3. Ullmann and Kipper [4] condensed 5-methoxy-2-chlorobenzoic acid with aniline in this way :

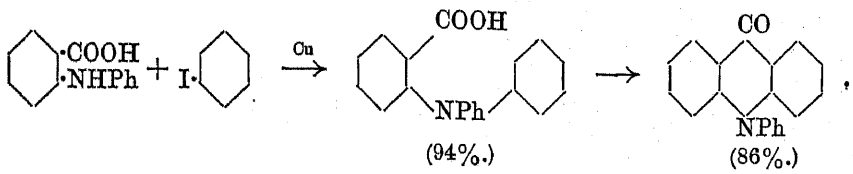


The following year Irma Goldberg [5] obtained phenylanthranilic acid quantitatively from anthranilic acid and bromobenzene, and Ullmann and Maag [6] similarly condensed *p*-dibromobenzene

[1] *Ber.*, 1892, **25**, 1733; *Ann.*, 1893, **276**, 35.
[2] Errera and Maltese, *Gazz.*, 1905, **35**, ii, 370.
[3] Cuttitta, *ibid.*, 1906, **36**, i, 325.
[4] *Ber.*, 1905, **38**, 2125.
[5] *Ibid.*, 1906, **39**, 1691.
[6] *Ibid.*, p. 1693.

with two molecular proportions of anthranilic acid. The method has been used for the preparation of a large number of acridones.

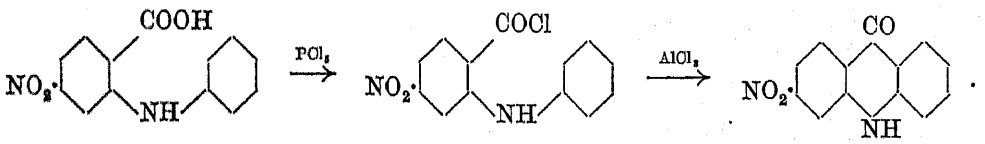
Phenylanthranilic acid fails to react with bromobenzene, but iodobenzene gives a 94% yield of diphenylanthranilic acid [1]:



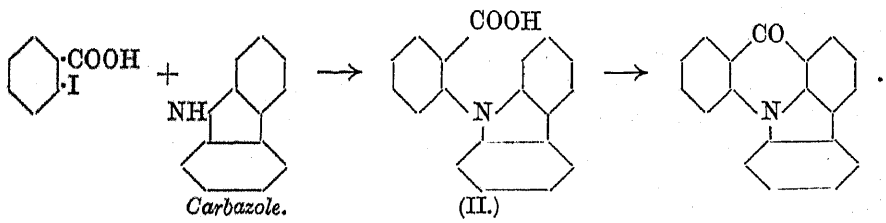
(94%.) (86%.)

The ethoxy-group in *p*-phenetylanthranilic acid is hydrolysed to ·OH during acridonation, whereas the methoxy group in *o*-anisylanthranilic acid remains.[2]

In certain cases acridonation does not proceed smoothly in the presence of H_2SO_4 and the arylanthranilic acid must first be converted into the acid chloride with PCl_5 or $SOCl_2$, the ring being then closed by the action of $AlCl_3$. This method is preferable in the preparation of nitroacridones [3]:

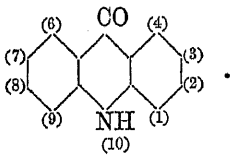


N-*o*-Carboxyphenylcarbazole (II), prepared from carbazole and *o*-iodobenzoic acid, is acridonated by the action of $ZnCl_2$ at 280°, or by successive treatment with PCl_5 and $AlCl_3$ [4]:



Carbazole. (II.)

The following acridones have been obtained from arylanthranilic acids. Where the reference number is italicised the Ullmann-Goldberg method was used for the preparation of the intermediate acid.



[1] Goldberg and Nimerowski, *Ber.*, 1907, **40**, 2448.
[2] Ullmann, *Ann.*, 1907, **355**, 344, 346.
[3] Ullmann, Bader and Labhardt, *Ber.*, 1907, **40**, 4795.
[4] Eckert, Seidel and Endler, *J. pr. Chem.*, 1922, **104**, 85.

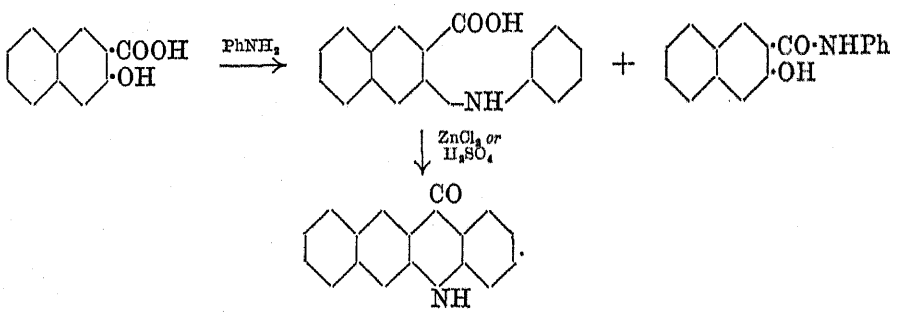
	References.
Acridone.	2, 3, 4, 9, *10*, *15*, *15a*, *18*, 22
1 : 2 : 3 : 4-Tetrahydroacridone.	22
10-Phenylacridone.	17
1-Methylacridone.	3, 6, 9, *10*, *18*
3-Methylacridone.	3, 5, 9, *10*, *18*
4-Methylacridone.	*10*, *18*
1 : 3-Dimethylacridone.	7, *10*, *18*
1-Chloroacridone.	*10*, *18*
2-Chloroacridone.	*19*
3-Chloroacridone.	*10*, *18*
4-Chloroacridone.	*10*, *18*
1 : 3-Dichloroacridone.	*10*, *18*
3-Bromoacridone.	*10*, *18*
3-Aminoacridone.	*10*, *18*
1-Nitroacridone.	*10*, *18*, *20*
2-Nitroacridone.	*19*, *21*
4-Nitroacridone.	*10*, *18*
1 : 3-Dinitroacridone.	1, *21*, *23*
3-Hydroxyacridone.	*10*, *18*
2 : 4-Dihydroxyacridone.	8, 12, 26
1-Methoxyacridone.	*10*, *18*
2-Methoxyacridone.	*19*
3-Methoxyacridone.	*11*
4-Methoxyacridone.	*24*
1-Carboxyacridone.	*10*, *18*
3-Carboxyacridone.	*10*, *18*
1 : 3-Dinitro-7-chloroacridone.	1
1 : 3 : 8-Trinitro-7-methylacridone.	13
1 : 3 : 6-Trinitro-7-methylacridone.	14

References.

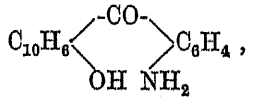
[1] Jourdan, *Ber.*, 1885, **18**, 1444. [2] Graebe and Lagodzinski, *ibid.*, 1892, **25**, 1733. [3] Pictet and Hubert, *Arch. Sciences, nat. phys.*, 1893, 215. [4] Graebe and Lagodzinski, *Ann.*, 1893, **276**, 35. [5] Graebe and Kahn, *ibid.*, 1894, **279**, 272. [6] Graebe and Locher, *ibid.*, p. 278. [7] Graebe and Kaufmann, *ibid.*, p. 285. [8] v. Niementowski, *Ber.*, 1896, **29**, 76. [9] Pictet and Hubert, *ibid.*, p. 1189. [10] D.R.-P. 145189. [11] Ullmann and Kipper, *Ber.*, 1905, **38**, 2125. [12] Baczyński and v. Niementowski, *ibid.*, p. 3009. [13] Errera and Maltese, *Gazz.*, 1905, **35**, ii, 370. [14] Cuttitta, *ibid.*, 1906, i, 325. [15] Goldberg, *Ber.*, 1906, **39**, 1691. [15a] Ullmann and Ernst, *ibid.*, p. 298. [16] Ullmann and Maag, *ibid.*, p. 1693. [17] Goldberg and Nimerowski, *ibid.*, 1907, **40**, 2448. [18] Ullmann, *Ann.*, 1907, **355**, 312–358. [19] Ullmann and Wagner, *ibid.*, pp. 359–371. [20] Ullmann and Maag, *Ber.*, 1907, **40**, 2522. [21] Ullmann, Bader and Labhardt, *ibid.*, p. 4795. [22] Borsche and Tiedtke, *ibid.*, 1908, **41**, 2203; 1909, **42**, 624. [23] Schroeter and Eisleb, *Ann.*, 1909, **367**, 101. [24] Kliegl and Fehrle, *Ber.*, 1914, **47**, 1636. [25] Suchanek, *J. pr. Chem.*, 1914, **90**, 475, 486. [26] Baczyński and v. Niementowski, *Ber.*, 1919, **52**, 461. [27] Eckert and Seidel, *J. pr. Chem.*, 1921, **102**, 338. [28] Eckert, Seidel and Endler, *J. pr. Chem.*, 1922, **104**, 85.

(b) *Naphthacridones:*

In the naphthalene series the *ortho*-arylamino-carboxylic acids are obtainable either from hydroxynaphthoic acids or from naphthaquinones. Thus Schöpf [1] prepared a "linear" naphthacridone from the anilide of β-hydroxynaphthoic acid:



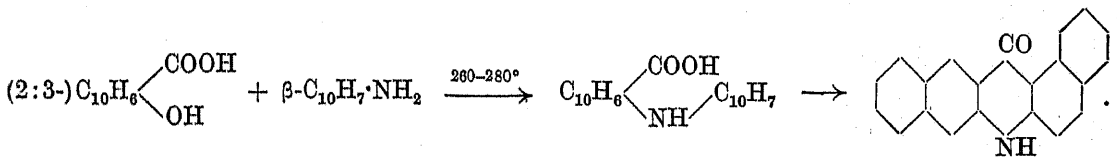
Both anilides equally give the naphthacridone, the normal anilide being probably converted first into the phenylnaphthylamine carboxylic acid. (Schöpf suggested an isomerisation to



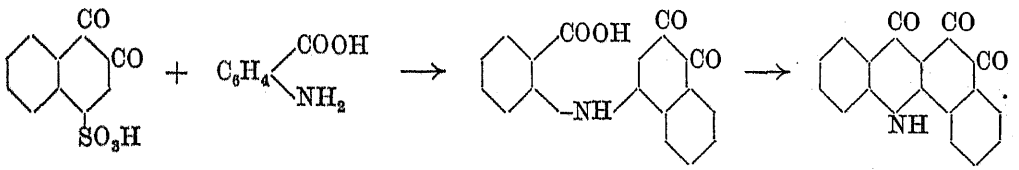
similar to that occurring in the flavaniline synthesis (*q.v.*), but this seems unnecessary.)

[1] *Ber.*, 1892, **25**, 2740; 1893, **26**, 1122, 2589.

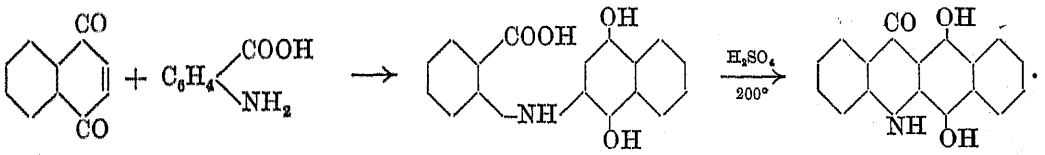
By the action of ammonia on β-hydroxynaphthoic acid at 260–280° Möhlau [1] obtained a dinaphthacridone, which Strohbach [2] prepared more easily in 28% yield from β-hydroxynaphthoic acid and β-naphthylamine. The latter base is formed intermediately in Möhlau's reaction:



By the condensation of β-naphthaquinone-4-sulphonic acid with anthranilic acid Lagodzinski and Hardine [3] prepared a naphthylanthranilic acid which was readily acridonated by means of H_2SO_4:

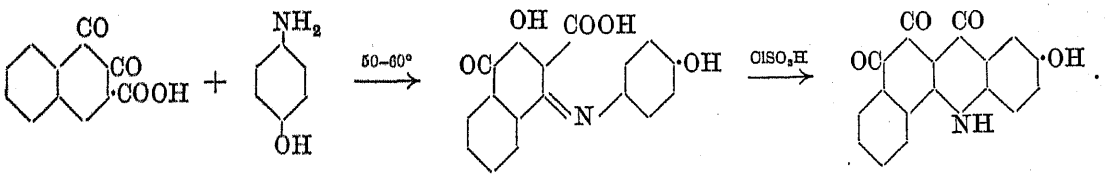


The ease with which quinones of the benzene and naphthalene series form anilides was taken advantage of by Hauschke [4] in the preparation of a "linear" naphthacridone:

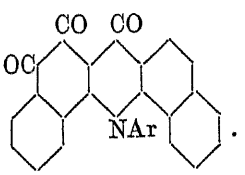


(76% yield.)

The quinone from β-hydroxynaphthoic acid condenses with *p*-aminophenol, according to D.R.-P. 290064, to give an anilide which is converted by chlorosulphonic acid into a naphthacridone:

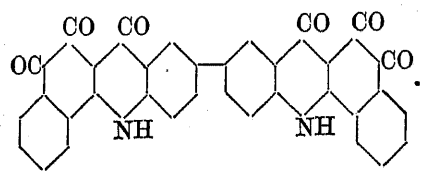


Similar condensations occur when α-naphthylamine and its phenyl- or *p*-anisyl-derivatives are used in place of *p*-aminophenol, the products being of the type:



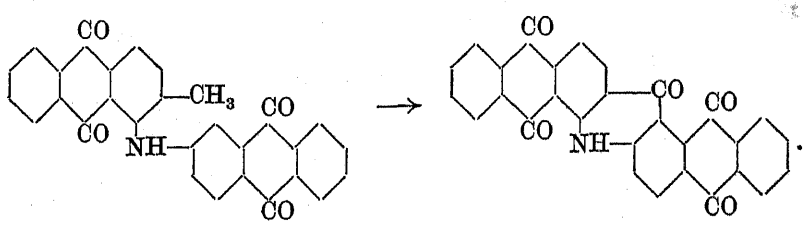
[1] *Ber.*, 1895, **28**, 3096.
[2] *Ibid.*, 1901, **34**, 4146.
[3] *Ibid.*, 1894, **27**, 3068.
[4] *J. pr. Chem.*, 1914, **90**, 451, 464, 466.

Benzidine gives a double acridone :

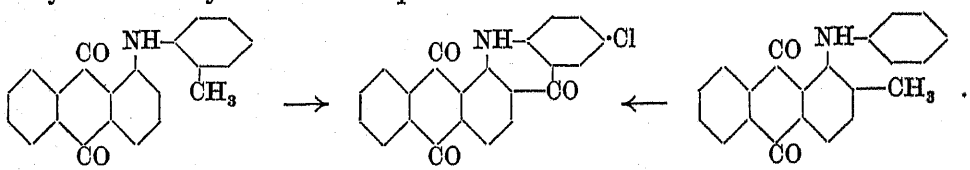


(c) *Anthracridones :*

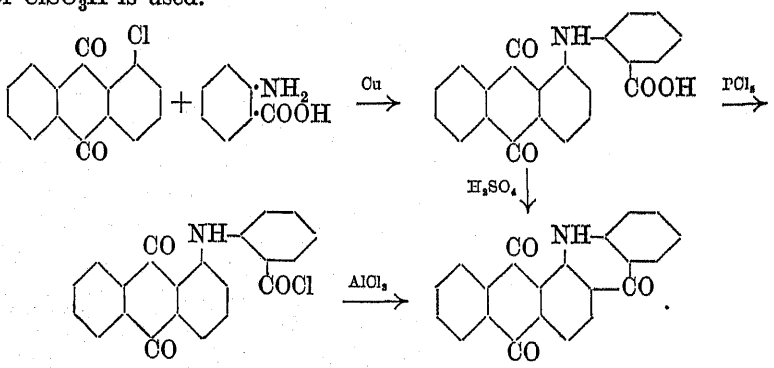
In the anthracene series the process of "acridonation" has been the subject of a large number of patents, several valuable vat dyestuffs being obtained in this way. In one of the earliest of these patents [1] 2-methyl-1 : 2-dianthrimide is oxidised and acridonated by alkaline fusion :



Chlorination or bromination of *o*-methyl-arylaminoanthraquinones at 160–175° also results in the formation of acridones, halogenation of the aryl group occurring at the same time. The methyl may be in the aryl or the anthraquinone nucleus [2] :



The anthraquinonylanthranilic acids may be acridonated directly by conc. H_2SO_4 or chlorsulphonic acid, or alternatively may be converted first into the acid chlorides, which give acridones on treatment with $AlCl_3$. Both methods have been investigated by Ullmann.[3] The second method gives a purer product and avoids the sulphonation which frequently occurs when H_2SO_4 or $ClSO_3H$ is used.



[1] D.R.-P. 192436.

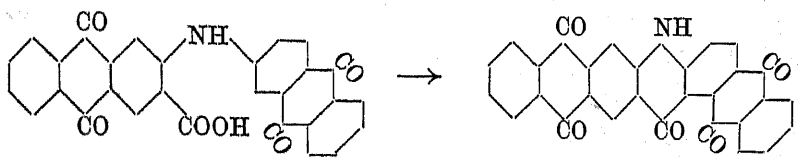
[2] D.R.-PP. 272296, 275671, 283724.

[3] Ullmann and Sone, *Ann.*, 1911, **380**, 336, 340; Ullmann and Ochsner, *ibid.*, 1911, **381**, 6, 9, 10; Ullmann and Billig, *ibid.*, p. 22; D.R.-P. 243586; Ullmann and Dootson, *Ber.*, 1918, **51**, 13–24.

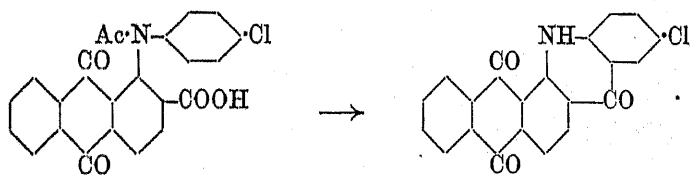
The yield by the direct method is 94%; by the $AlCl_3$ method 93%. By simply boiling the acid chloride in nitrobenzene a 76% yield of very pure acridone is obtained. From 1 : 5-dichloroanthraquinone the yield of chloro-acridone is 70% by H_2SO_4, 78% *via* the acid chloride. 1 : 4-Dichloroanthraquinone gives similar results.

Acridonation by sulphuric acid or $ClSO_3H$ is claimed for a variety of substituted anthraquinonylanthranilic acids in D.R.-PP. 221853, 240002, 241442, 245875, 256626, 258561 and 287614. According to the last-mentioned patent anthraquinone-β-sulphonic acids are used, the sulphonic group being afterwards eliminated either by reduction or by heating the product in a solvent.[1]

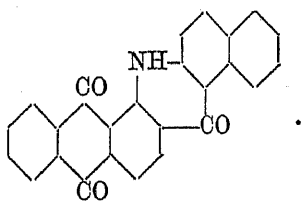
The ·COOH group may be in the anthraquinone nucleus. Thus [2]:



Acetylated 1-arylaminoanthraquinone-2-carboxylic acids are acridonated quantitatively by heating alone or in a solvent at 180–185° [3]:



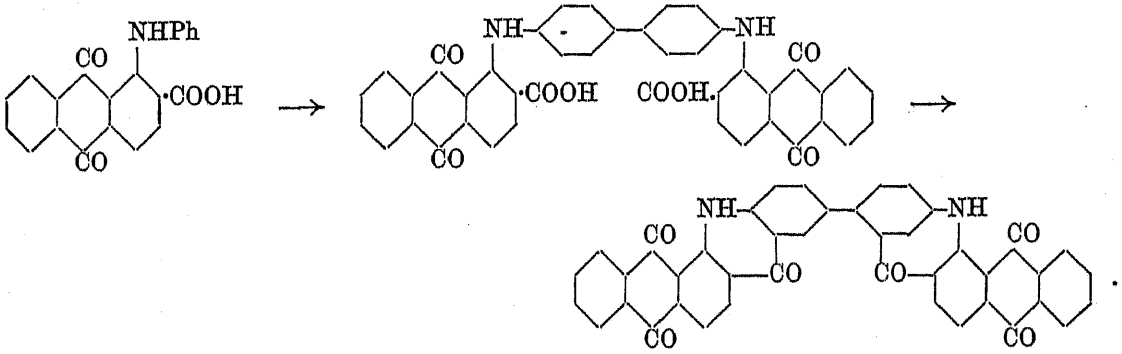
Apparently the acetyl group is so readily hydrolysed off that it functions as a dehydrating agent. 1-β-Naphthylaminoanthraquinone-2-carboxylic acid similarly gives



Brass [4] found that when α-arylaminoanthraquinones are oxidised by MnO_2 and H_2SO_4

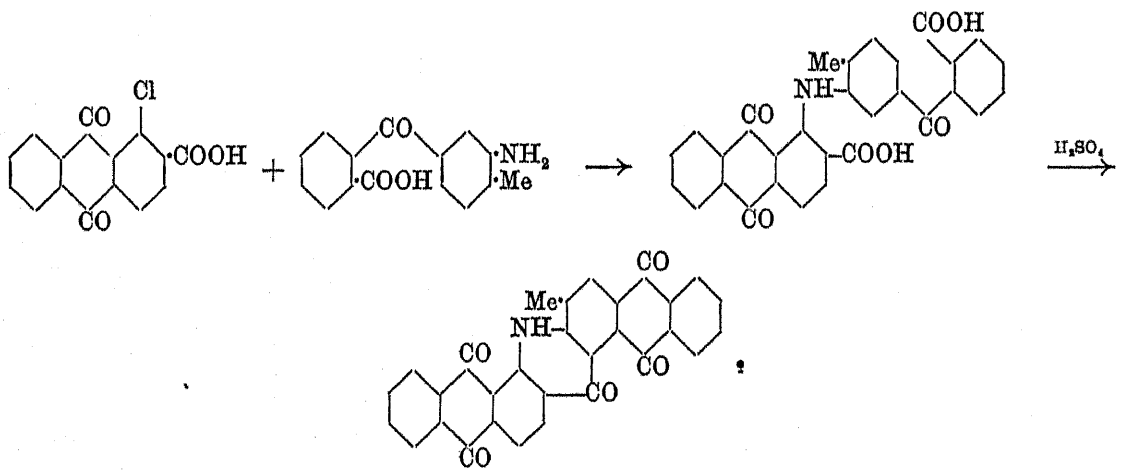
[1] D.R.-P. 287615.
[2] D.R.-P. 268219.
[3] D.R.-P. 248170.
[4] *Ber.*, 1913, **46**, 2911; D.R.-P. 268646.

at 13°, diphenyl derivatives are formed. If the aryl or anthraquinone nucleus carries an *ortho*-COOH group, the product may be acridonated by H_2SO_4 at 100–110° :

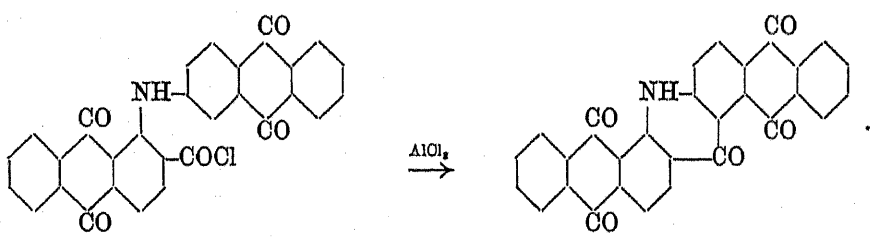


The same compound is obtained from α-anthraquinonylanthranilic acid. 1-*o*-Tolylamino-anthraquinone-2-carboxylic acid behaves similarly.

Acridonation and the conversion of a benzoyl-*o*-benzoic acid into an anthraquinone are combined in a single operation in the method of D.R.-P. 237546 :

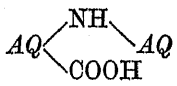


The acid chloride and $AlCl_3$ method of acridonation is claimed in D.R.-PP. 221853 and 237236; it is especially applicable to those intermediates in which the ·COOH is attached to the anthraquinone nucleus, *e.g.* :

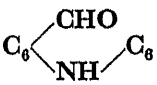


Acid chlorides of this type are acridonated by heating alone or in a solvent at 120–160° [1] or in the process of " vatting " with alkaline hydrosulphite at 70°.[2]

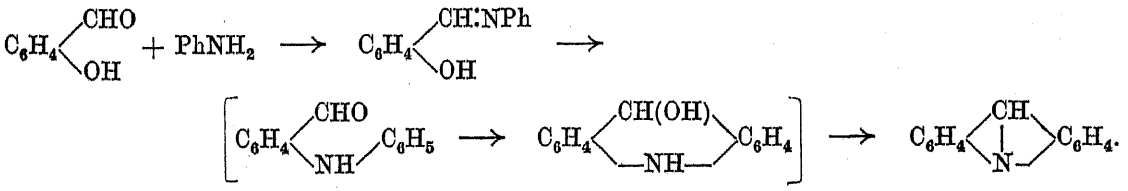
The preparation of dianthrimide-*o*-carboxylic acids



(where *AQ* stands for the anthraquinone residue) is usually difficult owing to a great tendency to lose CO_2.[3] This is diminished by using chalk or $BaCO_3$ as condensing agent, but is completely avoided by employing the esters instead of the free acids. The dianthrimide-*o*-carboxylic esters so obtained [4] are acridonated by $ClSO_3H$ at 35–40° [5] or during " vatting." [6]

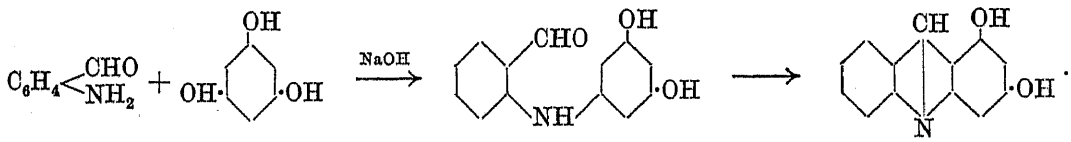
15. From aryl-*o*-amino-aldehydes : 

Closely related to the formation of acridones from arylanthranilic acids is the conversion of the corresponding aldehydes into acridines. Just as salicylic acid and aniline give acridone, salicylaldehyde and aniline at 260° yield acridine [7] :



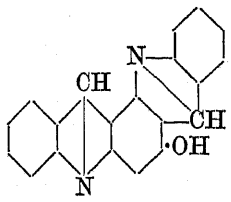
Möhlau's synthesis may, of course, be interpreted in several ways, but the above scheme agrees best with generally accepted views upon " acridination " in the anthracene series (see below, and following section).

Eliasberg and Friedländer's preparation of 2 : 4-dihydroxyacridine [8] from *o*-aminobenzaldehyde and phloroglucinol and v. Niementowski's further condensation products from the same substances [9] are analogous to the preparation of the corresponding acridones from anthranilic acid and phloroglucinol (see previous section) :

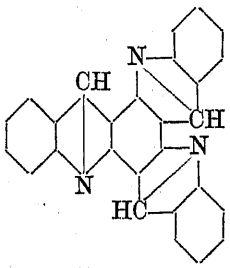


[1] D.R.-PP. 237237, 248966. [2] D.R.-P. 237237. [3] Schalk, *Dissn. Darmstadt*, 1911.
[4] D.R.-PP. 240327, 254475, 256344. [5] D.R.-P. 243586. [6] D.R.-P. 246966.
[7] Möhlau, *Ber.*, 1886, **19**, 2451. [8] *Ibid.*, 1892, **25**, 1758. [9] *Ibid.*, 1906, **39**, 386.

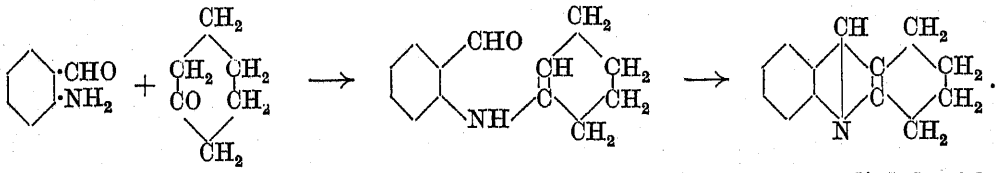
From two and three molecular proportions of *o*-aminobenzaldehyde the products are :



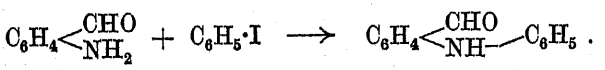
and



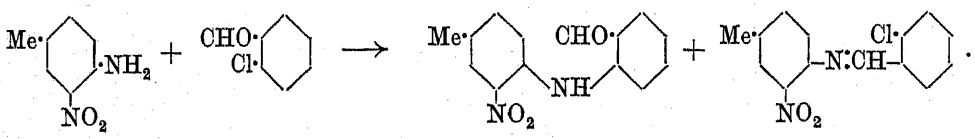
Borsche [1] obtained tetrahydroacridine by heating *o*-aminobenzaldehyde with *cyclo*hexanone either for some time at 130°, or better for 24 hours in alcoholic solution with the addition of a few drops of 10% aqueous NaOH :



Aryl-*o*-aminobenzaldehydes and their acridination products have been studied by Mayer [2] in an investigation of the products claimed in D.R.-P. 280711. Aniline and *o*-chlorobenzaldehyde gave no *o*-aldehydo-diphenylamine, but from iodobenzene and *o*-aminobenzaldehyde the desired product was obtained (in an impure state) and was easily converted into acridine by means of H_2SO_4 :

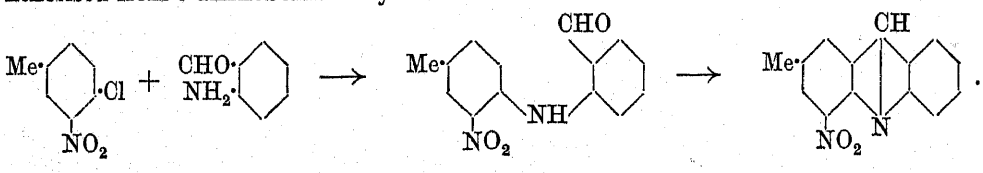


When *o*-chlorobenzaldehyde was heated with an aromatic amine, Na_2CO_3 and copper, a mixture of *o*-aldehydodiphenylamine and Schiff's base (an azomethine) usually resulted. In the benzene series it was found that azomethine formation was hindered by the presence of a nitro group *ortho* to the $\cdot NH_2$ and the diphenylamine was then the main product. Thus :



(Main product.) *Azomethine.*

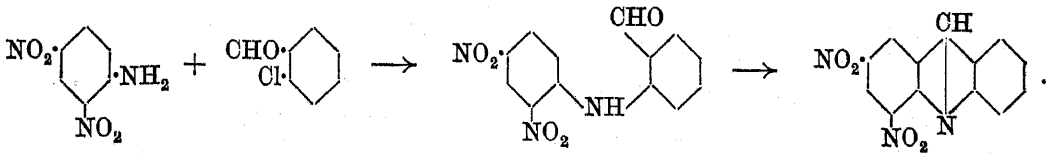
From the mixture, by the action of H_2SO_4, 3-methyl-1-nitroacridine was obtained. This was also synthesised from *o*-aminobenzaldehyde :



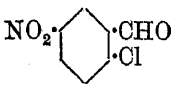
[1] *Ber.*, 1908, **41**, 2203.

[2] Mayer and Kalischer, *ibid.*, 1916, **49**, 1994; Mayer and Stein, *ibid.*, 1917, **50**, 1306; Mayer and Lewis, *ibid.*, 1919, **52**, 1641.

2 : 4-Dinitroaniline and *o*-chlorobenzaldehyde gave no azomethine, but a pure dinitro-aldehydo-diphenylamine, from which 1 : 3-dinitroacridine was readily prepared :

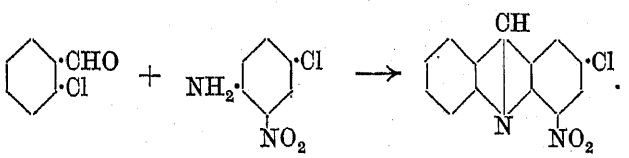


o-, *m*- and *p*-Chloroanilines, 2 : 4-dichloroanilines, 2 : 4 : 6-trichloroaniline, 2-chloro-4-nitro-aniline, 3-chloro-*p*-toluidine, 2-aminofluorene, 2-aminofluorenone, 2-nitro-7-aminofluorene, 4-nitro-*α*-naphthylamine and 1-nitro-*β*-naphthylamine all gave only azomethines when condensed with *o*-chlorobenzaldehyde. Even 5-nitro-2-chlorobenzaldehyde

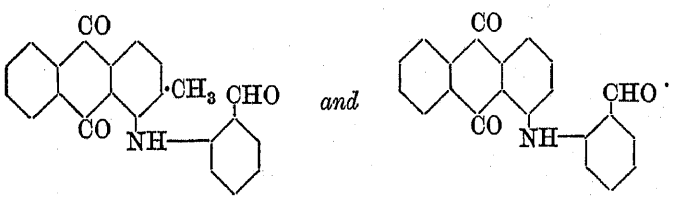


in which the chlorine atom should be very reactive, gave with *p*-chloroaniline only the Schiff base and with 2 : 4-dinitroaniline and 1-aminoanthraquinone no reaction at all.

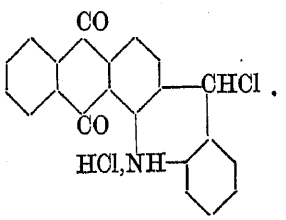
o-Chlorobenzaldehyde and 2-nitro-4-chloroaniline yield the nitrochloroacridine when heated together at 100° :



1-Amino-2-methylanthraquinone and *α*-aminoanthraquinone [1] also react with *o*-chloro-benzaldehyde in the desired direction, giving

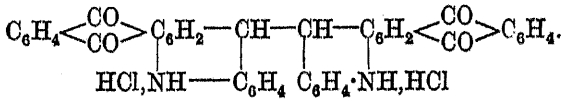


The former could not, of course, be acridinated, but from the latter by boiling with acetic acid and HCl a compound containing chlorine was obtained, to which Mayer and Stein assigned the structure :

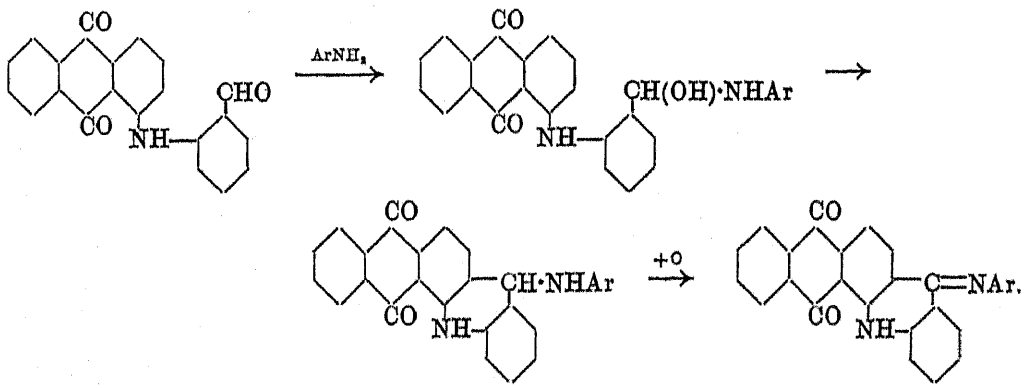


[1] D.R.-P. 280711.

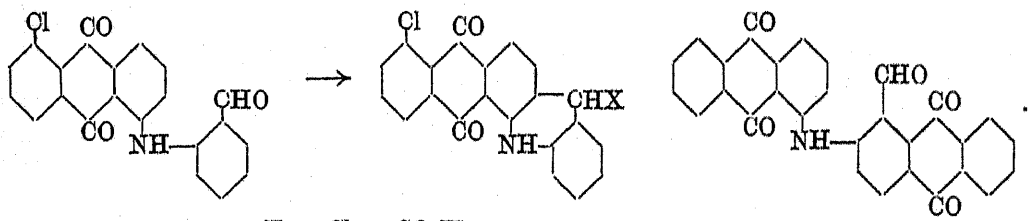
The dyestuff of D.R.-P. 280711, prepared by heating together *o*-chlorobenzaldehyde, *α*-aminoanthraquinone, potassium acetate and cuprous chloride in naphthalene, is apparently derived from this by condensation of two molecules with loss of Cl_2 and perhaps oxidation to a stilbene :



Acridination of *o*-aldehydophenyl-*α*-aminoanthraquinone was brought about by Kalischer and Mayer,[1] by condensation with aniline or with *β*-aminoanthraquinone, mercuric sulphate being added as oxidant :



An analogous compound, in which Ar = *α*-anthraquinonyl, was actually isolated from the products of the process described in D.R.-P. 280711, and was synthesised in the above manner, using *α*-aminoanthraquinone, by Mayer and Lewis. 5-Chloro-1-aminoanthraquinone behaves in the same way. An interesting result was obtained by treating the condensation product (I) from *o*-chlorobenzaldehyde and 1 : 5-aminochloroanthraquinone with HCl (in acetic acid) or conc. H_2SO_4 :

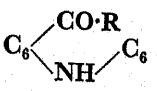


(I.) (X = ·Cl or ·SO_4H). (II.)

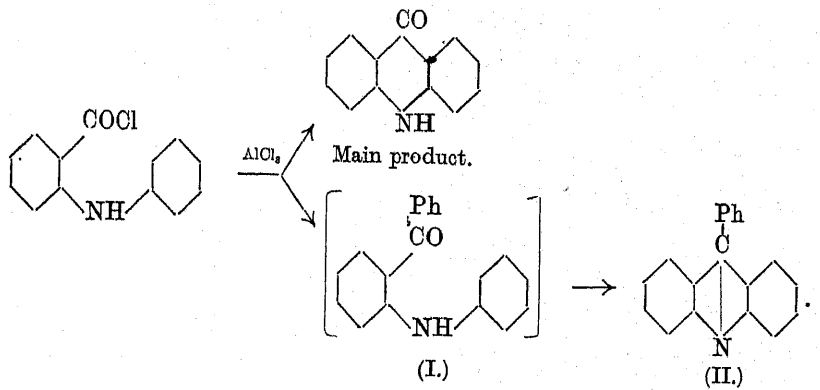
The product (II) from 2-chloro-1-aldehydoanthraquinone and *α*-aminoanthraquinone gave a similar sulphate with conc. H_2SO_4.

These compounds are strong confirmation of the view of the reaction given on p. 367, for they are simply the hydrochloric and sulphuric esters corresponding to the final intermedate there figured, namely dihydroacridol.

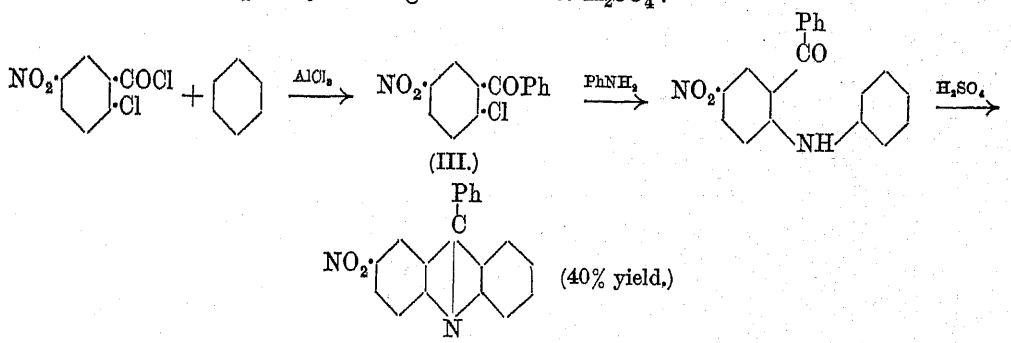
[1] *Ber.*, 1916, **49**, 1994.

16. From aryl-*o*-aminoketones: 

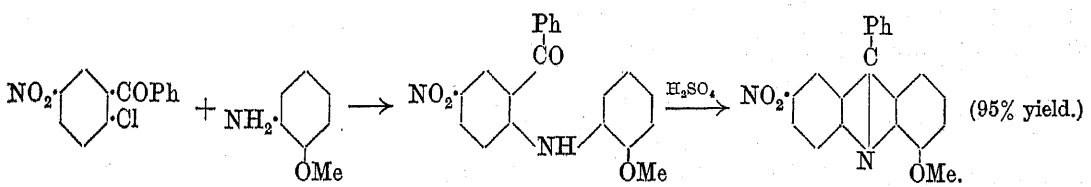
Ullmann and Ernst [1] obtained 5-phenylacridine (II) as a by-product of the action of $AlCl_3$ upon *o*-phenylaminobenzoyl chloride. *o*-Phenylaminobenzophenone (I) is probably first formed, but could not be isolated:



5-Phenylacridine forms only 2–3% of the product, but Ullmann and Ernst were able to obtain substituted acridines in fairly good yield by first synthesising the appropriate *o*-phenylaminobenzophenone and subsequently treating it with conc. H_2SO_4:

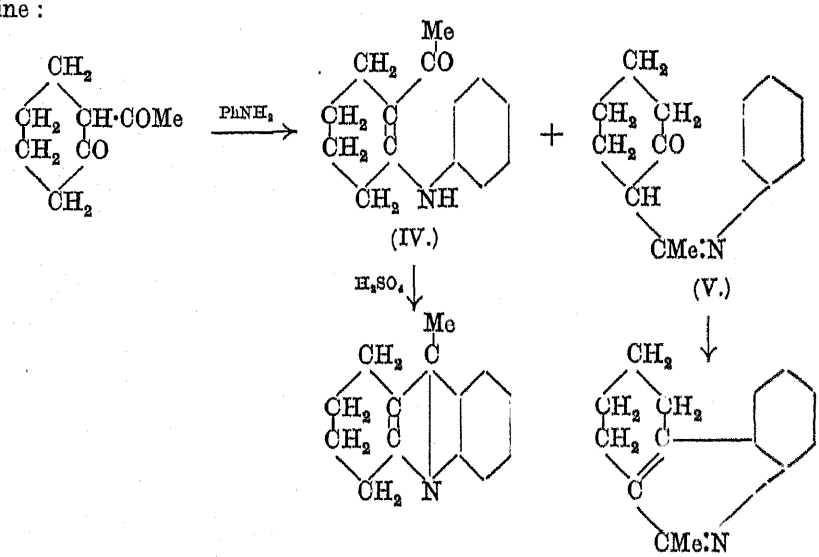


The substitution of sodium acetate for H_2SO_4 raised the yield of 3-nitro-5-phenylacridine to 80%, and it was found that the product could be obtained in one operation from nitrochlorobenzophenone (III) by heating with sodium acetate and aniline. *o*-Anisidine, *p*-phenylenediamine and *α*- and *β*-naphthylamines reacted similarly, though the first of these gave only 20% yield. The methoxynitroacridine is obtained almost quantitatively by the two-stage process:



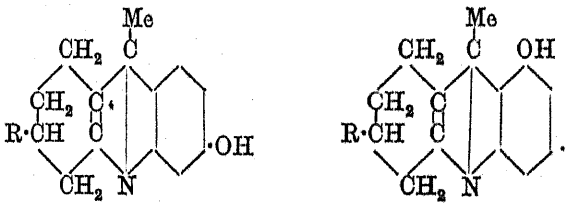
[1] *Ber.*, 1906, **39**, 298.

A similar reaction was used by Borsche [1] for the preparation of tetrahydroacridines. Thus α-acetyl*cyclo*hexanone (from *cyclo*hexanone, acetic ester and sodium) condenses with aniline in glacial acetic acid to give a difficultly separable mixture of anilides (IV and V). These are converted by conc. H_2SO_4 at 100° into 5-methyltetrahydroacridine and the corresponding phenanthridine :



(IV.) (V.)

m-Aminophenol gives only one anilide (type IV) with acetyl*cyclo*hexanone and with 2-acetyl-5-methyl*cyclo*hexanone. Treatment with H_2SO_4 gives the acridine derivatives (VI) :

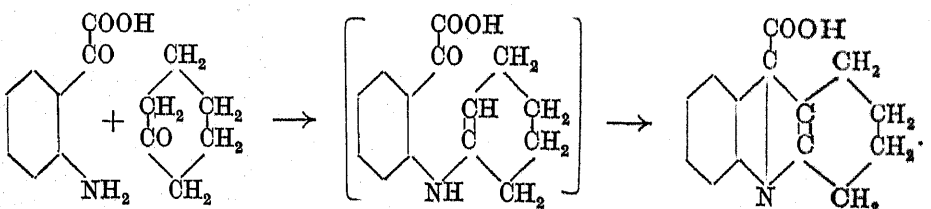


(R = H, Me.)

(VI.) (VII.)

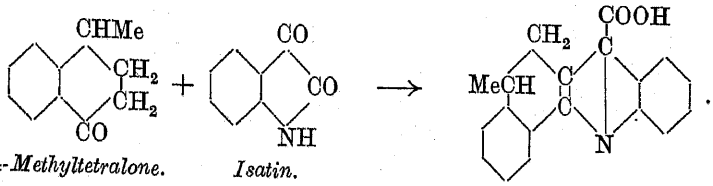
There seems to be no tendency to form the isomeric 6-hydroxy compound (VII).

In a further synthesis of the same type Borsche [2] avoided the formation of phenanthridines by using an *o*-aminoketone (in place of aniline, etc.) and *cyclo*hexanones (in place of their acetyl derivatives). One of the most readily accessible *o*-aminoketones is isatic acid (or its anhydride, isatin), and this was found to give tetrahydroacridine-5-carboxylic acid in 90% yield when warmed for 24 hours with 33% KOH and *cyclo*hexanone [3] :



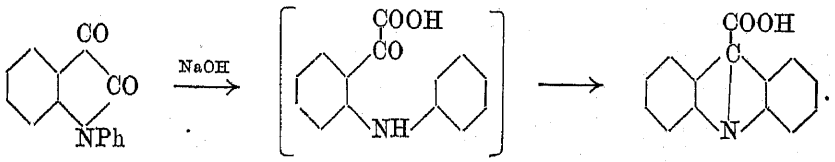
[1] *Ber.*, 1908, **41**, 2203; *Ann.*, 1910, **377**, 89–122. [2] *Loc. cit.* [3] D.R.-P. 290703.

The reaction is quite general. *cyclo*Pentanone and *cyclo*heptanone yield homologous ring compounds of the same type,[1] and v. Braun and Stückenschmidt [2] have recently obtained "4-methyltetrophan" and "3-methyltetrophan" from isatin and the corresponding tetralones:



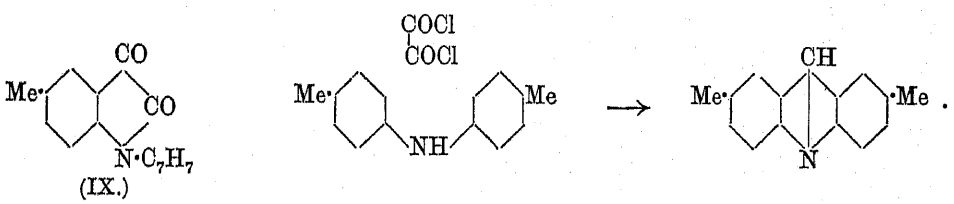
4-Methyltetralone. *Isatin.* *4-Methyltetrophan.*

Stollé [3] in his investigation of the aryloxamic chlorides (see Indoles, p. 101) observed the formation of acridines in certain cases. Friedländer and Kunz [4] had shown that *N*-phenylisatin, boiled with NaOH, was converted into acridine-5-carboxylic acid (VIII):



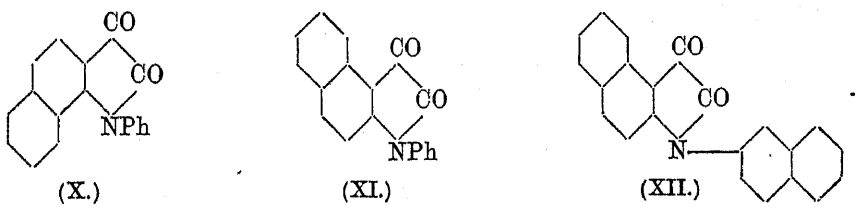
(VIII.)

Stollé found that diphenylamine and oxalyl chloride treated with $AlCl_3$ gave not only *N*-phenylisatin but the acid chloride corresponding to (VIII). *N*-*p*-Tolyl-5-methylisatin (IX) gives no acridine when heated with NaOH, but di-*p*-tolylamine and oxalyl chloride readily yield the corresponding dimethylacridine (·COCl being lost as CO_2 and HCl):



(IX.)

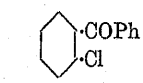
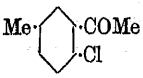
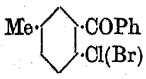
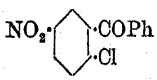
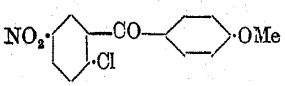
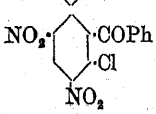
N-Phenyl-*α*-naphthisatin (X), *N*-phenyl-*β*-naphthisatin (XI) and *N*-*β*-naphthyl-*β*-naphthisatin (XII) give the corresponding acridines in the normal manner with boiling NaOH, but the oxalyl chloride method gave only the isatins and no acridines.



(X.) (XI.) (XII.)

[1] Borsche, *loc. cit.*
[2] *Ber.*, 1923, **56**, 1724.
[3] *J. pr. Chem.*, 1922, **105**, 137–148.
[4] *Ber.*, 1922, **55**, 1605.

The following arylaminoketones have been converted into acridines and naphthacridines *:

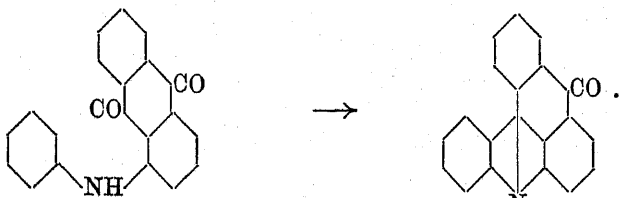
Arylaminoketone from			*References.*
	+	*o*-Nitroaniline. 3-Nitro-*p*-toluidine. 2 : 4-Dinitroaniline. 2-Nitro-4-chloroaniline.	7
	+	Iodobenzene. *α*-Bromonaphthalene. *β*-Bromonaphthalene.	7
	+	2 : 4-Dinitroaniline.	7
	+	2 : 4-Dinitroaniline. 3-Nitro-*p*-toluidine.	7
	+	Aniline. *o*-Anisidine. *α*- and *β*-Naphthylamines. *p*-Phenylenediamine.	1
	+	Aniline.	1
	+	Aniline. *o*-Aminophenol. *α*-Naphthylamine. *p*-Phenylenediamine (single and double).	2
2-Acetyl*cyclo*hexanone	+	Aniline. *m*-Aminophenol.	3
2-Acetyl-5-methyl*cyclo*hexanone	+	Aniline. *m*-Aminophenol.	3
α-Acetyl-camphor	+	*m*-Aminophenol.	3
*cyclo*Hexanone	+	Isatin. Dibromoisatin.	3, 4 3
3-Methyl*cyclo*hexanone	+	Isatin. Dibromoisatin. *o*-Aminoacetophenone.	3
4-Methyl*cyclo*hexanone	+	Isatin. Dibromoisatin.	3
Pulegone	+	Isatin. Dibromoisatin.	3
4-Methyltetralone	+	Isatin.	8
3-Methyltetralone	+	Isatin.	8
N-Phenylisatin			5, 6
Diphenylamine	+	Oxalyl chloride.	5
Di-*p*-tolylamine	+	Oxalyl chloride.	5
N-Phenyl-*α*-naphthisatin			5
N-Phenyl-*β*-naphthisatin			5
N-*β*-Naphthyl-*β*-naphthisatin			5

* For acridinations in the anthraquinone series, see next page.

References.

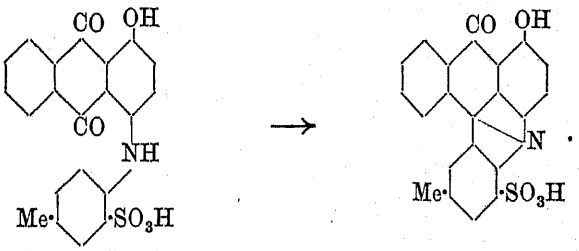
[1] Ullmann and Ernst, *Ber.*, 1906, **39**, 298. [2] Ullmann and Broido, *ibid.*, p. 356. [3] Borsche, *ibid.*, 1908, **41**, 2203; *Ann.*, 1910, **377**, 89–122. [4] D.R.-P. 290703. [5] Stollé, *J. pr. Chem.*, 1922, **105**, 137–148. [6] Friedländer and Kunz, *Ber.*, 1922, **55**, 1605. [7] Mayer and Freund, *ibid.*, pp. 2054–58. [8] v. Braun and Stückenschmidt, *ibid.*, 1923, **56**, 1724.

In the anthraquinone series α-arylamino derivatives are converted into acridines by treatment with conc. H_2SO_4.[1] The ring-closure occurs in exactly the same way as with the aryl-*o*-amino-ketones and -aldehydes described above and in the preceding section. Thus:



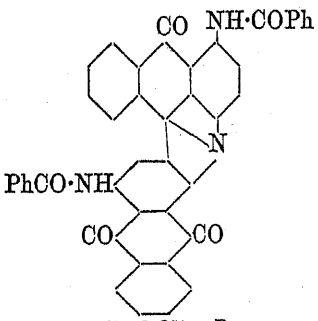
Phenyl-α-amino-anthraquinone.

The constitution of the products was elucidated by Dammann and Gattermann.[2] The reaction has been applied to a large number of substituted α-aminoanthraquinones and appears to be quite general. Friedländer and Schick [3] "acridinated" Alizarin Irisole:



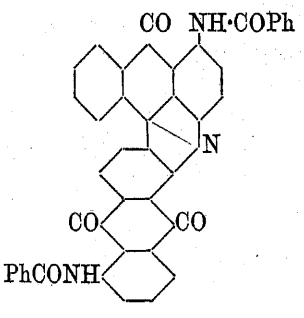
Alizarin Irisole.

while arylated 1 : 4- and 1 : 5-diaminoanthraquinones undergo a double condensation. The reaction has even been extended to "dianthrimides," Algol Brown R and Algol Olive R being acridinated products of this type [4]:



Algol Olive R.

[1] D.R.-P. 126444.
[3] *Ibid.*, 1903, **2**, 430.



Algol Brown R.

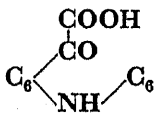
[2] *Z. Farb. Text. Chem.*, 1902, **1**, 325.
[4] D.R.-P. 239544.

Phosphoric acid at 160° may be used in place of H_2SO_4 in the acridination of phenyl-α-amino-anthraquinone,[1] and in some cases zinc chloride and glacial acetic acid bring about the coudensation.[2]

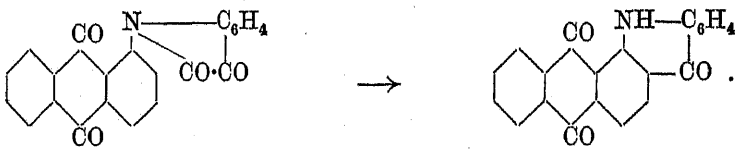
1-Arylamino-anthraquinone-2-carboxylic acids give acrid*ines* with sulphuric acid of 60° Bé. at 90–100°,[3] while with more concentrated H_2SO_4 the products are acrid*ones* (see next section).

Other acridinations in the anthraquinone series are described in D.R.-PP. 258808, 265725, 268454, 269194,[4] 272614 and 330572.

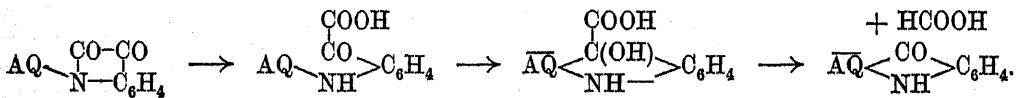
17. From *N*-α-anthraquinonylisatins:



The elimination of ·CO· from certain *N*-substituted isatins by the action of H_2SO_4* or $AlCl_3$ is described in D.R.-P. 286095 (1914):

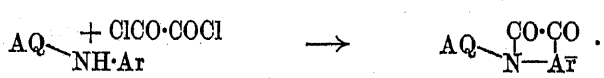


The same conversion into acridone is brought about by treating the isatin with NaOH and then "vatting" in the usual way with hydrosulphite. The course of the reaction seems to be as follows:



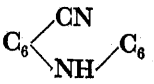
(AQ and $\overline{AQ}$ represent mono- and di-valent anthraquinone residues.)

The anthraquinonylisatins are obtained from α-chloroanthraquinones and isatin or from α-arylaminoanthraquinones and oxalyl chloride:

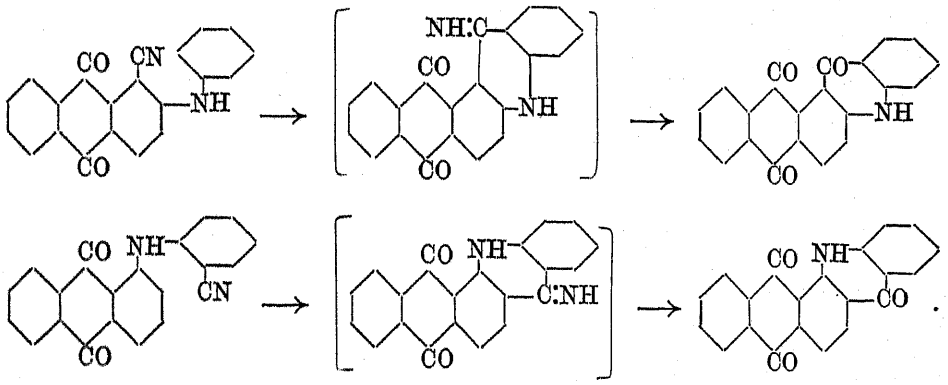


[1] D. Pat. Anm. F. 12993/1901.
[2] D.R.-PP. 126444, 269194.
[3] D.R.-P. 262469.
[4] E.P. 8143/1911.

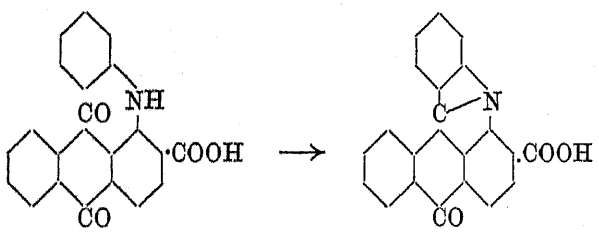
* Under other conditions H_2SO_4 converts anthraquinonylisatins into acridines as in Stollé's method (p. 373).

18. From arylaminoanthraquinone-*o*-nitriles: 

Acridones of the anthraquinone series are obtained by treating with H_2SO_4 an arylamino anthraquinone in which a ·CN group is *ortho* to the ·NH· either in the aryl or the anthraquinon nucleus.[1] Thus:



The advantage of this method is that there is much smaller tendency to form acrid*ines* than i the case of the carboxylic acids. Phenyl-1-aminoanthraquinone-2-carboxylic acid is easil converted into the acridine [2]:



but the products from 1-arylamino-2-cyanoanthraquinones consist almost entirely of th acridones.

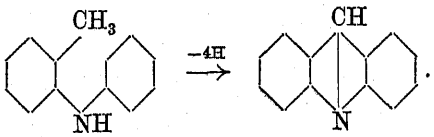
β-Cyanoanthraquinones are difficult to prepare, but 1-amino-2-bromoanthraquinone i readily converted by the Sandmeyer reaction into the 1-cyano-2-bromo-derivative. This is hydr lysed by ammonia, but with aniline and even more readily with *α*- or *β*-aminoanthraquinon it condenses without hydrolysis.

[1] Schaarschmidt, *Ann.*, 1914, **405**, 95.

[2] D.R.-PP. 126444, 239544.

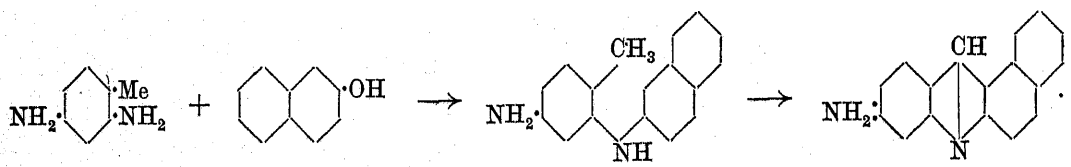
19. From *o*-methyldiphenylamine derivatives : $C_6\langle^{CH_3}_{NH}\rangle C_6$

By passing the vapours of *o*-tolylaniline through a hot tube Graebe [1] obtained considerable quantities of acridine :



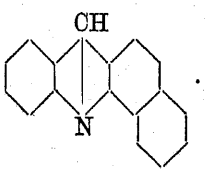
Di-*o*-tolylamine similarly gave 1-methyl-acridine.

Oxidation with sulphur leads to a similar acridine synthesis from *m*-tolylenediamine and *α*- or *β*-naphthol or -naphthylamine.[2] The mixture of bases (or base and naphthol) is heated with $ZnCl_2$ and sulphur at 180–190° and gives a yield of about 20% :

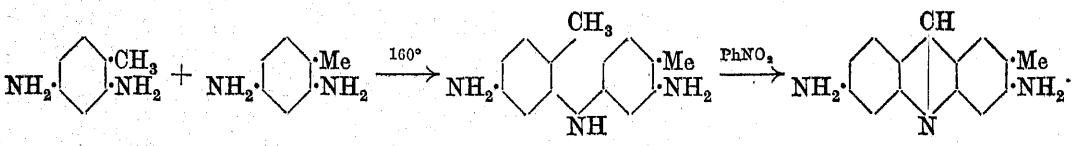


β-naphthacridine.

From *α*-naphthol or *α*-naphthylamine the product is :



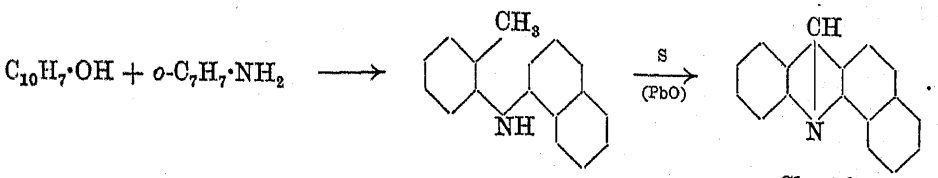
Nitrobenzene has also been used as an oxidant [3] :



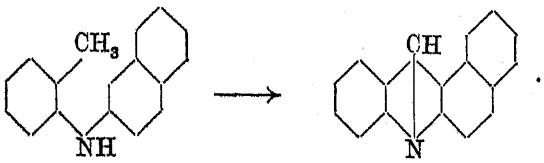
The 2 : 4-tolylenediamine may be replaced by the 2 : 6-isomer or by 4 : 6-diaminoxylene. Alternative constitutions for the products are possible in each case.

[1] *Ber.*, 1884, **17**, 1370. [2] D.R.-P. 130360. [3] D.R.-P. 258560.

Ullmann and La Torre [1] similarly obtained phenonaphthacridine from *o*-tolyl-α- and β-naphthylamines by oxidation with PbO or sulphur, the yields being 60% for the α- and 25% for the β-compound. The products are identical with Pictet and Erlich's α- and β-Chrysidines (see p. 352):

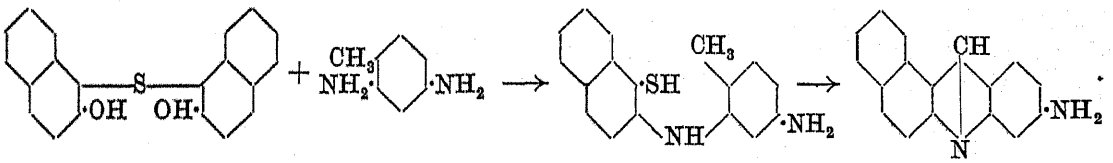


α-Chrysidine.



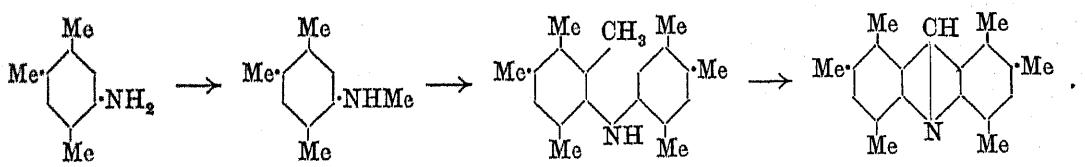
β-Chrysidine.

The thio-di-β-naphthol prepared from β-naphthol and sulphur gives with *m*-tolylenediamine a 20% yield of an aminophenonaphthacridine [2]:



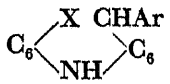
Amino-β-chrysidine.

When the hydrochlorides of certain aromatic amines, especially xylidines, are methylated with MeOH at high temperatures (270–300°), methyl groups wander to the nucleus and give mesidine and ψ-cumidine; in addition there is formed a small quantity (4–5%) of methylated acridines. Thus Liebermann and Kardos [3] obtained tetra- and hexa-methylacridines from 4- and 5-*m*-xylidine, di-, tri- and tetra-methylacridines from *m*-toluidine, and hexamethylacridine from ψ-cumidine:

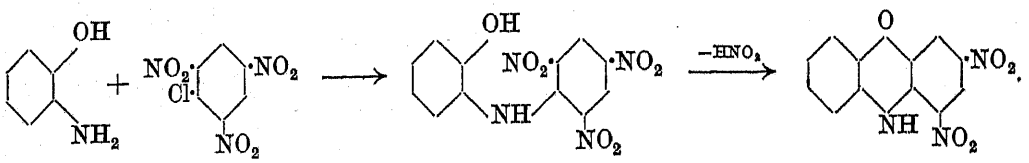


ψ-Cumidine.

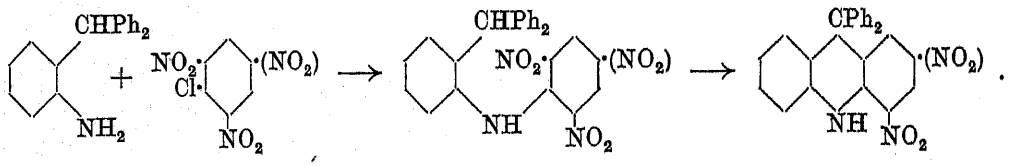
[1] *Ber.*, 1904, **37**, 2922.
[2] Ullmann and Bühler, *Z. Farb. Text. Chem.*, 1905, **4**, 521.
[3] *Ber.*, 1913, **46**, 208; 1914, **47**, 1563.

20. From *o*-aminotriarylmethanes and picryl chloride etc.: 

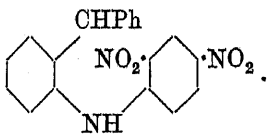
Turpin obtained a dinitrophenoxazine from *o*-aminophenol and picryl chloride:



Kehrmann, Ramm and Schmajewski [1] have devised a similar synthesis for dihydroacridines ("carbazines"), the ·OH of the *o*-aminophenol being replaced by a ·$CHAr_2$ group. *o*-Aminotriphenylmethane reacts readily with 2 : 6-dinitro- or 2 : 4 : 6-trinitro-chlorobenzene, and the secondary amine so formed gives a dihydroacridine when boiled with quinoline:

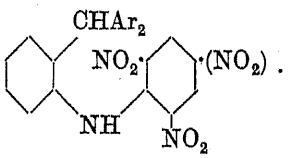


2 : 4-Dinitrobromobenzene gives the secondary amine

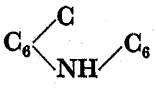


but no ring-closure occurs on subsequent treatment with quinoline.

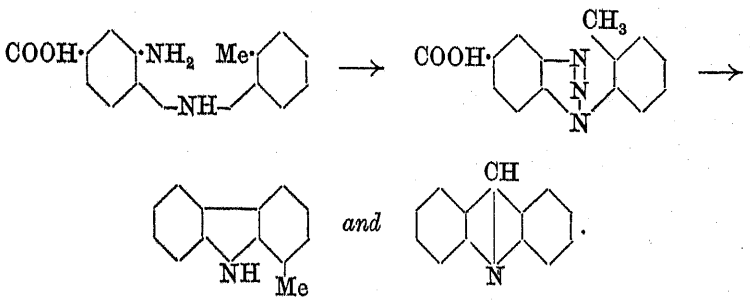
The reaction also fails when the group ·$CHPh_2$ is replaced by ·CH_3, ·CH_2Ph or ·$CHMe_2$, but is stated to be general for compounds of the type



[1] *Helv. Chim. Acta*, 1921, **4**, 538.

21. As by-product in Ullmann's carbazole synthesis: 

In the decomposition of *o*-tolylaziminobenzenes by heat there is formed in addition to the 4-methylcarbazole an appreciable quantity of acridine:[1]

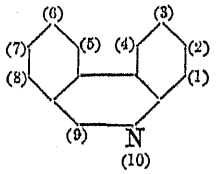


4-*m*-Xylylaziminobenzoic acid similarly gives 3-methylacridine.

[1] Ullmann, *Ann.*, 1904, 332, 82; Delétra and Ullmann, *Zentr.*, 1904, i, 1568.

CHAPTER XI

PHENANTHRIDINES AND OTHER POLYNUCLEAR PYRIDINE DERIVATIVES,



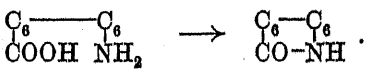
Phenanthridine.

Introductory :

Syntheses leading to phenanthridine or its derivatives may be grouped as follows.

I. *From diphenyl derivatives :*

The most important synthesis in this group is the conversion of phenanthraquinone into *phenanthridone via* o-aminodiphenyl-*o'*-carboxylic acid (sect. 1).



A method which recalls Bernthsen's acridine synthesis is Pictet and Hubert's dehydration of o-acylaminodiphenyls, which leads to *phenanthridine* and its 9-substituted derivatives (sect. 2).

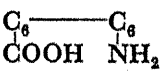
Phenanthridine is formed by dehydration of the oxime of *o*-aldehydodiphenyl (sect. 3) and *phenanthridone* from fluorenone-oxime by Beckmann change (sect. 3). The pyrrole ring of *N*-methylcarbazole is widened, with production of *phenanthridine*, when the compound is distilled (sect. 4).

II. *Ring-closure between the two benzene nuclei :*

The production of *phenanthridine* by distilling benzalaniline through a hot tube (sect. 5) gives poor results when extended to benzal-toluidines. Benzanilide yields *phenanthridone* (sect. 5).

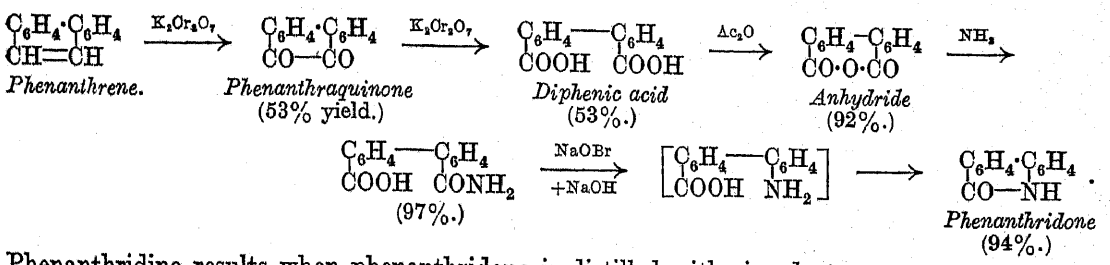
The linkage of the two nuclei may also be brought about by the Sandmeyer reaction; *e.g.* the diazo compound of *o*-aminobenzoylmethylaniline gives N-*methylphenanthridone* (sect. 6).

Dehydration of (side-chain) anils of 2-acetyl*cyclo*hexanones leads to *tetrahydrophenanthridines* (sect. 7).

1. From 2-aminodiphenyl-2-carboxylic acid: 

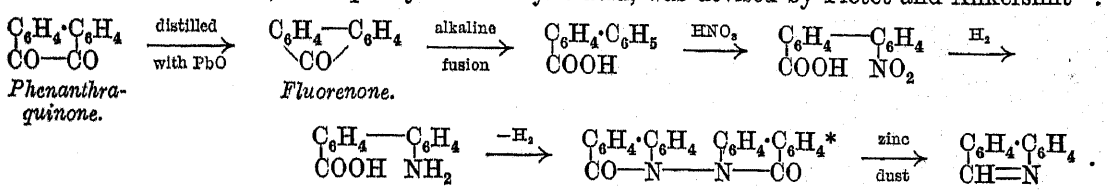
Phenanthrene has been converted into phenanthridine by three different methods. The first, *via* diphenic acid, is due to Graebe and Aubin,[1] and has recently been repeated by Oyster and Adkins [2]:

[1] *Ann.*, 1888, **247**, 257; Graebe and Wander, *ibid.*, 1893, **276**, 245.
[2] *J. A. C. S.*, 1921, **43**, 208.

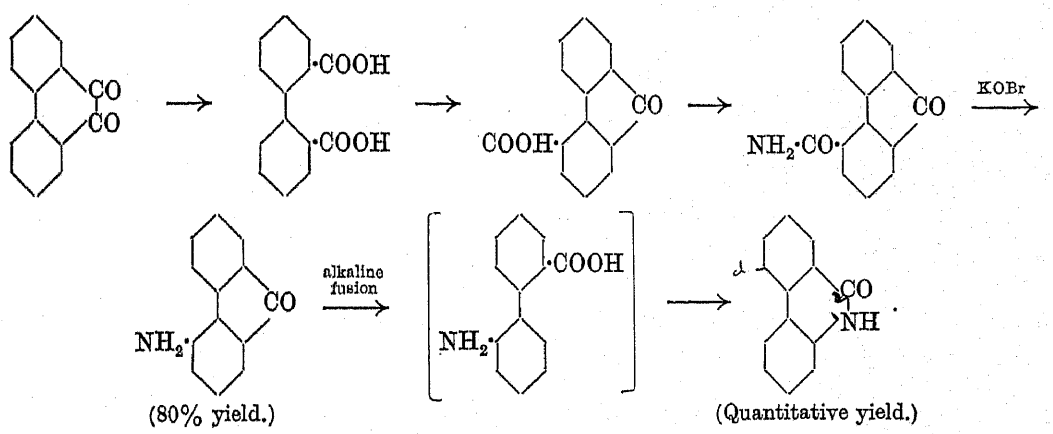


Phenanthridine results when phenanthridone is distilled with zinc dust.

The second method, *via* diphenyl-*o*-carboxylic acid, was devised by Pictet and Ankersmit [1]:

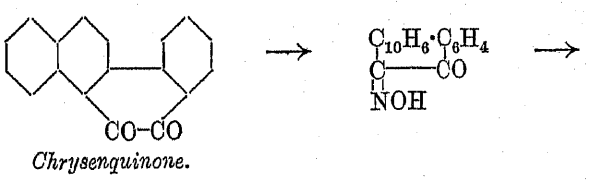


A very neat synthesis of phenanthridone from phenanthraquinone was achieved by Graebe and Schestakow [2]:

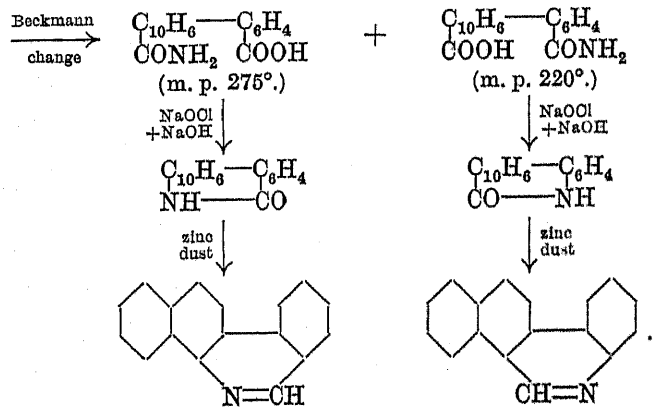


The quantitative yield in the last stage (showing that the fluorenone ring is broken in one direction exclusively) is unexpected.

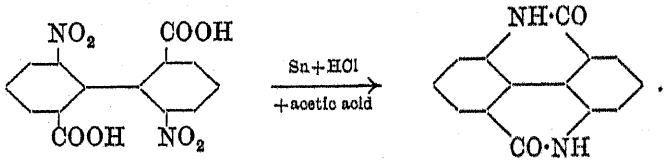
To the same group of syntheses belongs Graebe's preparation of naphthanthridines from chrysenquinone [3]:



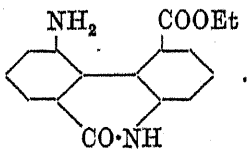
[1] *Ann.*, 1891, **266**, 142; *Ber.*, 1893, **26**, 1962; Graebe and Wander, *Ann.*, 1893, **276**, 245.
[2] *Ibid.*, 1895, **284**, 309, 312.
[3] Graebe and Hönigsberger, *ibid.*, 1900, **311**, 372; Graebe, *ibid.*, 1904, **335**, 126, 128.
* A certain amount of true phenanthridone is formed in this dehydration, but Pictet and Ankersmit's "phenanthridone" is the bimolecular oxidation product.

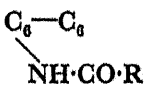


Kenner and Stubbings [1] have prepared the di-lactam of 2 : 6-diaminodiphenyl-2 : 6-dicarboxylic acid :

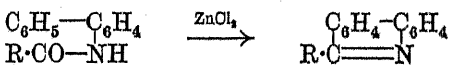


The corresponding dinitro-ester gives on reduction both the di-lactam and the lactam-amino-ester :



2. From acylated *o*-aminodiphenyl : 

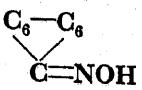
Pictet and Hubert [2] synthesised phenanthridines by dehydration of acyl-*o*-aminodiphenyls with $ZnCl_2$ at 250–300° :



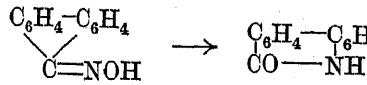
(R = H, Me, Et, Ph, ·OEt.)

The urethane (R = ·OEt) gives only a very small yield of phenanthridone.[3]

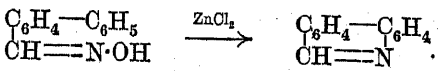
[1] *J. C. S.*, 1921, **119**, 601. [2] *Ber.*, 1896, **29**, 1182. [3] *Ibid.*, p. 1188.

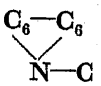
3. From fluorenone oxime etc.: 

Fluorenone oxime undergoes the usual Beckmann transformation with production of phenanthridone. Wegerhoff tried H_2SO_4 and PCl_5 without success, but Pictet [1] and Kerp [2] by using zinc chloride obtained a small yield of phenanthridone, which Pictet and Gonset [3] increased to 30%:

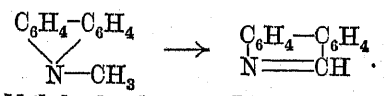


The closely related *o*-phenylbenzaldoxime gives phenanthridine by direct dehydration with $ZnCl_2$ at 280–300° [4]:



4. From *N*-methylcarbazole: 

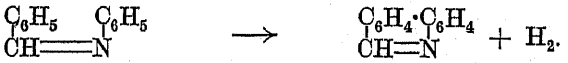
Just as alkylpyrroles give pyridines, so *N*-methylcarbazole is converted into phenanthridine by dry distillation. The yield is 40% [5]:



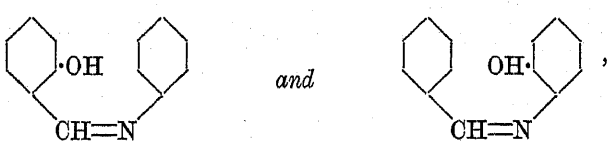
Methylcarbazole. *Phenanthridine.*

5. From benzalaniline: 

By passing the vapour of benzylidene-aniline through a hot tube Pictet and Ankersmit [6] obtained considerable amounts of phenanthridine:



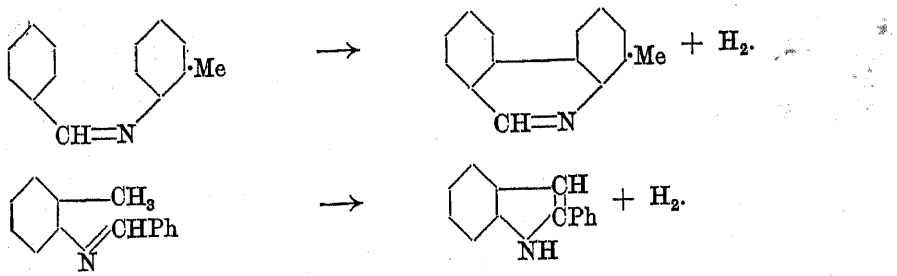
From the corresponding *o*-hydroxy compounds,



no phenanthridine could be prepared by the action of $ZnCl_2$, conc. H_2SO_4, P_2O_5 or acetic anhydride, while distillation with zinc dust gave only acridine.

[1] *Chem. Zeitung*, 1894, **18**, 1822. [2] *Ber.*, 1896, **29**, 230.
[3] *Arch. Sci. Gen.* 1897, **3**, 37; *Zentr.*, 1897, i, 413. [4] Pictet and Gonset, *loc. cit.*
[5] Pictet, *Ber.*, 1905, **38**, 1950. [6] *Ber.*, 1889, **22**, 3339; *Ann.*, 1891, **266**, 146.

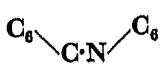
Benzal-*p*-toluidine is converted at red heat into the corresponding methylphenanthridine.[1] The *o*-toluidine derivative had previously been investigated by Etard,[2] but his product was shown by Pictet and Erlich to be 2-phenylindole (p. 148), the phenanthridine being obtainable only at a bright red heat (with much phenylindole):



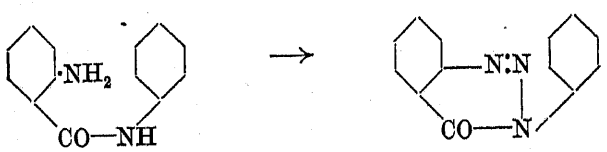
α- and *β*-Chrysidines obtained in the same way from *α*- and *β*-naphthylamines have been shown by Ullmann to be acridine derivatives (p. 352).

According to Pictet and Gonset,[3] benzanilide gives only a small quantity of phenanthridone when passed through a hot tube, but H. Meyer and Hofmann [4] were more successful:



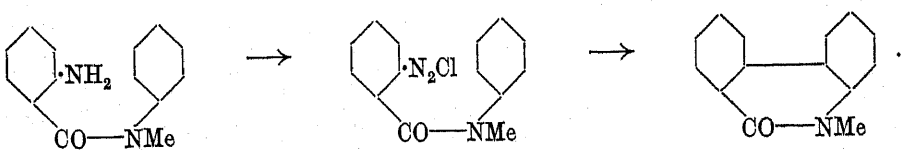
6. From o-aminobenzanilides: 

Ullmann's carbazole synthesis from phenylaziminobenzene suggests the synthesis of phenanthridone from *o*-aminobenzanilide, but the diazo-imide obtained by the action of nitrous acid does not decompose in the desired direction [5]:

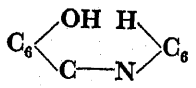


(*no phenanthridone*).

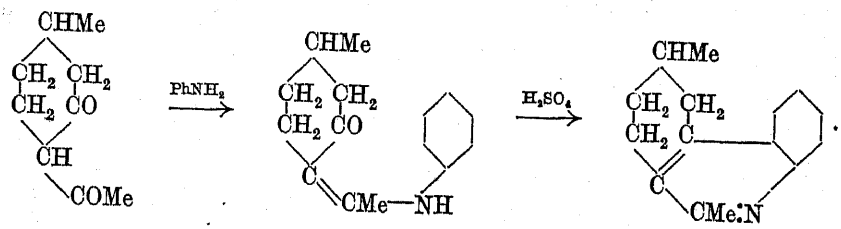
The alkylated anilides, however, can be converted into *N*-alkylphenanthridones by the action of heat on the corresponding diazo compounds:



[1] Pictet and Erlich, *Ann.*, 1891, **266**, 153.
[2] *Compt. rend.*, 1882, **95**, 730.
[3] *Zentr.*, 1897, i, 414.
[4] *Monatsh.*, 1916, **37**, 681.
[5] Pictet and Gonset, *Arch. Sci. Gen.*, 1897, **3**, 37; *Zentr.*, 1897, i, 413.

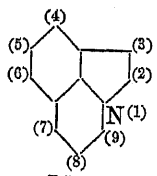
7. From α-acetylcyclohexanones: 

In the condensation of aniline, etc., with α-acetylcyclohexanone the $\cdot NH_2$ may react with either the cyclic or the side-chain carbonyl group. In the first case an acridine is obtained (p. 372), and in the second a phenanthridine. Usually the acridine predominates in the product [1]:

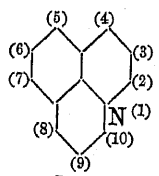


6:9-*Dimethyl*-5:6:7:8-*tetrahydrophenanthridine.*

LILOLE AND JULOLE



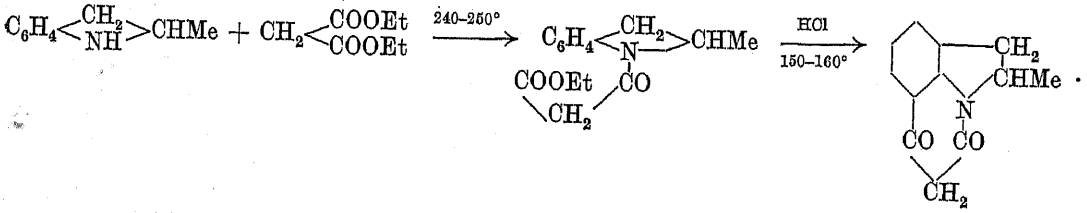
Lilole.



Julole.

1. Lilole derivatives:

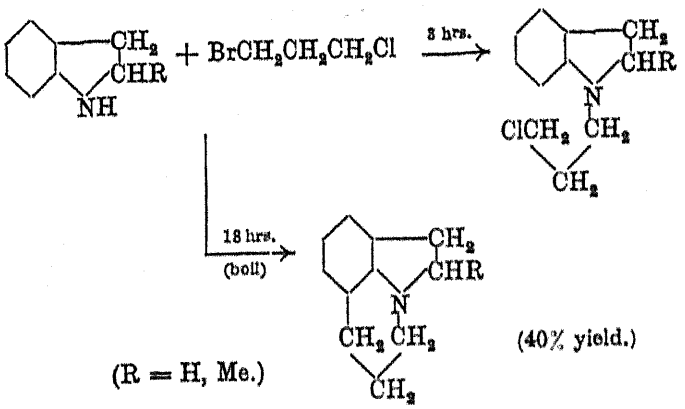
2-Methyl-7:9-diketolilolidine was prepared by Bamberger and Sternitzki [2] from α-methyldihydroindole and malonic ester:



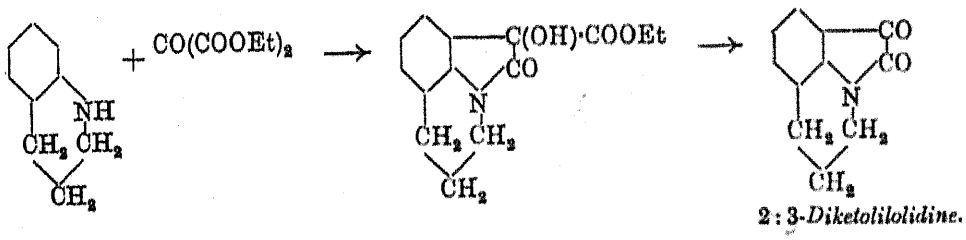
[1] Borsche, *Ann.*, 1910, 377, 80, 97.

[2] *Ber.*, 1893, 26, 1297.

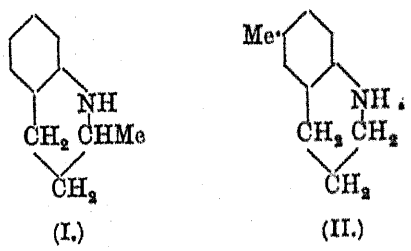
Lilolidine itself may be obtained from dihydroindole by the method used by Pinkus (see p. 389) for julolidine from tetrahydroquinoline.[1] α-Methyldihydroindole behaves similarly:



Martinet's dioxindole synthesis (see p. 139) when applied to tetrahydroquinoline leads to a lilolidine derivative [2]



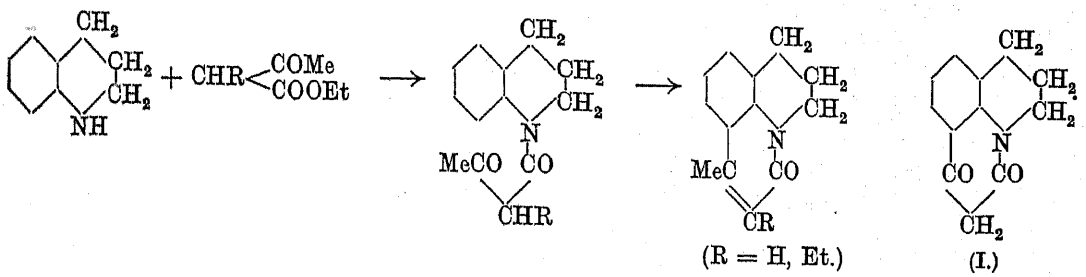
Tetrahydroquinaldine (I) and 6-methyltetrahydroquinoline (II) have also been condensed in this way with mesoxalic ester.



[1] v. Braun, Heider and Wyczatkowska, *Ber.*, 1918, **51**, 1219.
[2] Guyot and Martinet, *Compt. rend.*, 1913, **156**, 1625.

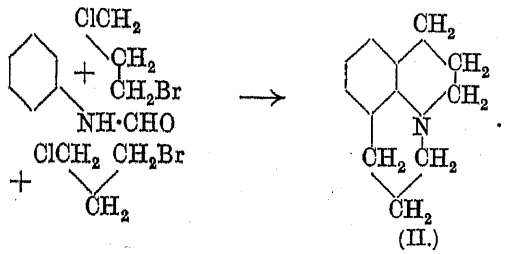
2. Julole derivatives :

The first compound of the julole type was prepared by Reissert in 1891 [1] from tetrahydroquinoline and acetoacetic ester. The corresponding 9-ethyl-8-methyl-10-ketojuloline is obtained from ethylacetoacetic ester [2]:

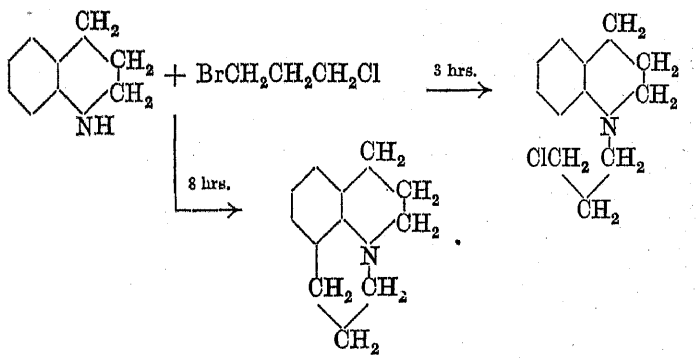


Malonic ester gives 8 : 10-diketojulolidine (I).

Pinkus [3] heated formanilide with trimethylene chlorobromide * and obtained julolidine (II). The formyl group is eliminated and a double ring-closure occurs in the two *ortho* positions :



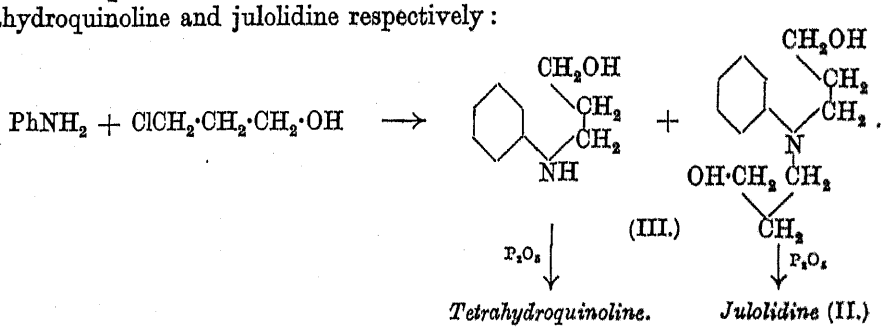
The method was improved by v. Braun, Heider and Wyczatkowska,[4] who heated tetrahydroquinoline for eight hours with trimethylene chlorobromide :



Rindfusz and Harnack [5] have prepared julolidine from aniline and trimethylene chloro-

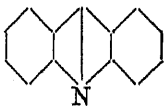
[1] Reissert, *Ber.*, 1891, **24**, 841. [2] *Idem, ibid.*, 1892, **25**, 1190.
[3] *Ibid.*, p. 2798. [4] *Ibid.*, 1918, **51**, 1224. [5] *J. A. C. S.*, 1920, **42**, 1720.
* He expected to obtain phenylpyrrolidone.

hydrin. The first product is a mixture of secondary bases (III), which are converted by P_2O_5 into tetrahydroquinoline and julolidine respectively:

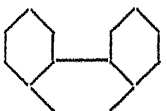


OTHER POLYNUCLEAR PYRIDINE DERIVATIVES

Besides acridine (I) and phenanthridine (II)

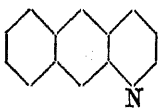


(I.)

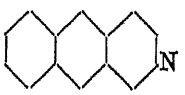


(II.)

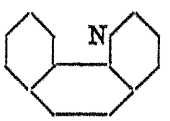
pyridine derivatives of the following polynuclear types have been prepared:



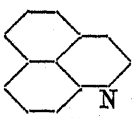
(III.)



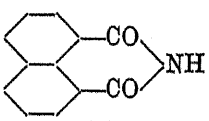
(IV.)



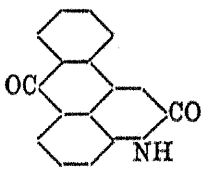
(V.)



(VI.)



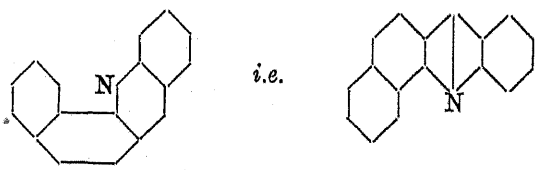
(VII.)



(VIII.)

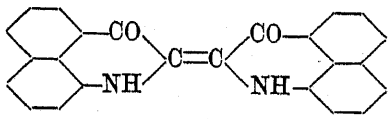
Formulæ III and IV represent anthrapyridines—benzoquinoline and benzo*iso*quinoline respectively—and must not be confused with the pyridanthrones (VIII), which are often loosely referred to as anthrapyridones.

No simple compounds of the type (V) have been prepared, but the acridine analogues



are well known; they are the α-naphthacridines (see Acridines).

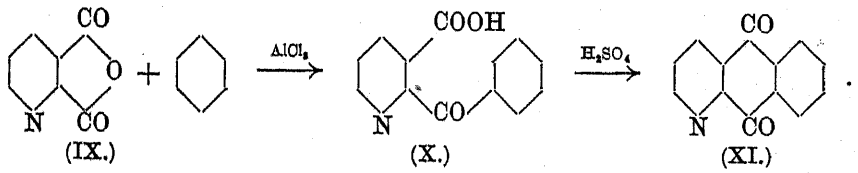
The substance (VII) is the parent of *peri*naphthindigo



peri-Naphthalimide (VII) is used for several vat-dyestuffs.[1]
The pyridanthrones (VIII) are discussed in Chapter VII (p. 238).

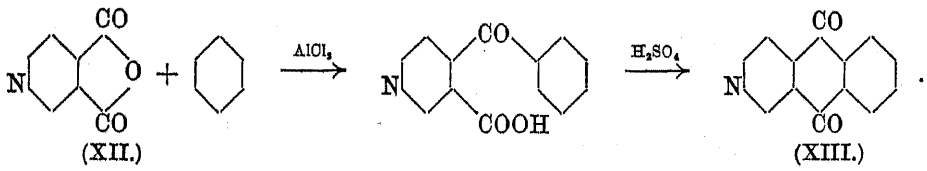
1. Anthrapyridines

Bernthsen and Mettegang [2] condensed quinolinic anhydride (IX) with benzene in the presence of $AlCl_3$ but failed to convert the product (X) into an anthrapyridine (XI). The experiment was repeated with little more success by Philips,[3] only a trace of the desired substance being produced :



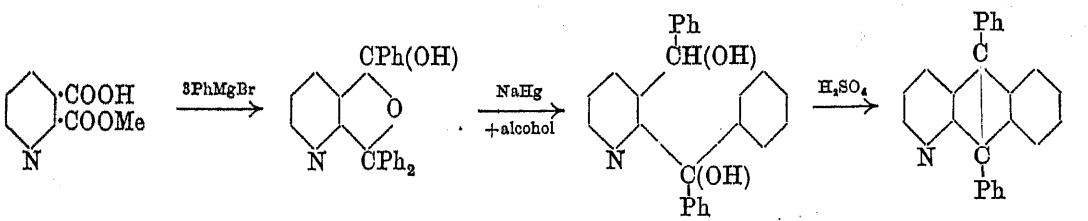
(IX.) (X.) (XI.)

A better result was obtained with cinchomeronic anhydride (XII), which gave a 12% yield of the anthrapyridine (XIII) [4] :



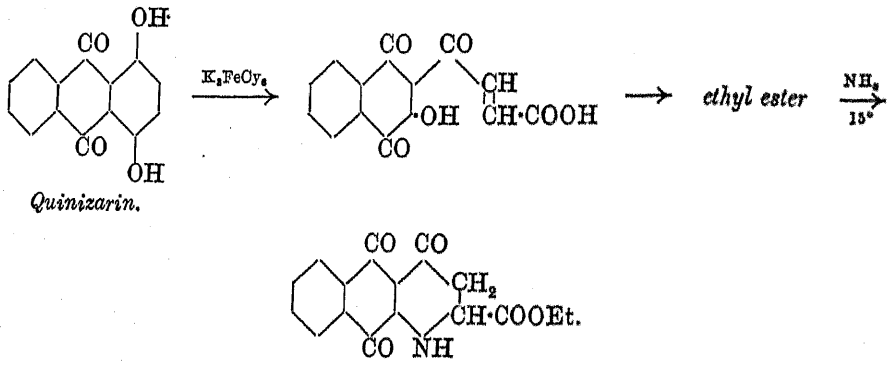
(XII.) (XIII.)

Simonis and Cohn [5] have prepared a *meso*diphenyl derivative of 1-anthrapyridine (III) by the following series of reactions :



[1] D.R.-PP. 276357, 276358, 276956.
[2] *Ber.*, 1887, **20**, 1209.
[3] *Ibid.*, 1894, **27**, 1923; 1895, **28**, 1658.
[4] Philips, *loc. cit.*
[5] *Ber.*, 1914, **47**, 1245.

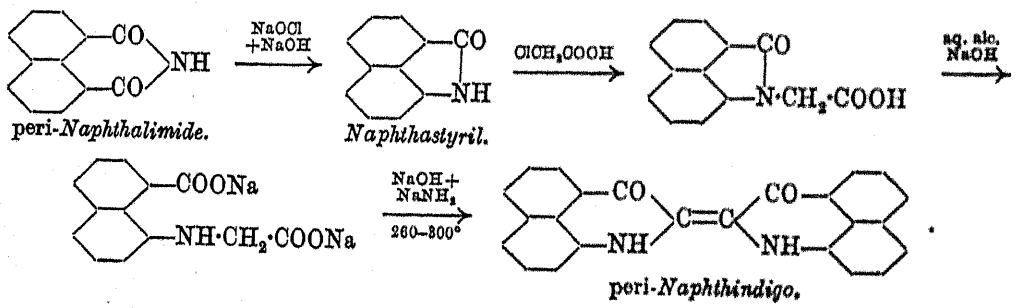
A triketo ester of the 1-anthrapyridine type was obtained by Scholl, Dahll and Hansgirg [1]:



Quinizarin.

2. *peri*-Naphthindigo

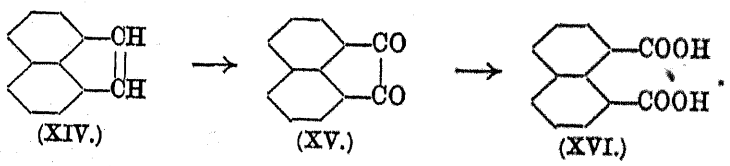
This compound is obtained from naphthastyril (p. 180) by condensation with chloroacetic acid, hydrolysis and alkaline fusion. Fierz and Sallmann [2] failed to obtain any *peri*-naphthindigo in this way, but Dutt [3] has been successful:



peri-*Naphthalimide.* *Naphthastyril.* peri-*Naphthindigo.*

3. *peri*-Naphthalimide

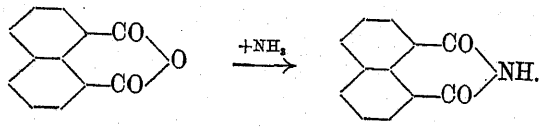
The starting material for *peri*-naphthalimides is acenaphthene (XIV) or its quinone (XV), either of which is readily oxidised to *peri*-naphthalic acid (XVI) [4]:



(XIV.) (XV.) (XVI.)

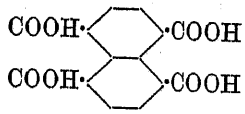
[1] *Ber.*, 1923, **56**, 2553. [2] *Helv. Chim. Acta*, 1922, **5**, 562. [3] *J. C. S.*, 1923, **123**, 224.
[4] Graebe and Gfeller, *Ber.*, 1892, **25**, 652; Ullmann and Cassirer, *ibid.*, 1910, **43**, 439.

peri-Naphthalimide is obtained by passing NH_3 into the molten anhydride [1] or by simply heating the anhydride with aqueous ammonia at 100° [2]:

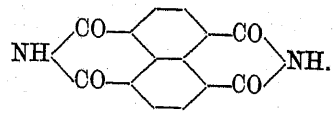


Methylamine, ethylamine, aniline, *o*-toluidine, benzylamine and hydroxylamine similarly yield *N*-substituted *peri*-naphthalimides.[3]

Bamberger and Philip [4] oxidised pyrene to the naphthalenetetracarboxylic acid (XVII), from the di-anhydride of which they prepared the di-imide (XVIII):



(XVII.)



(XVIII.)

[1] Behr and van Dorp, *Ann.*, 1874, **172**, 270.
[2] Jaubert, *Ber.*, 1895, **28**, 360.
[3] *Idem, loc. cit.*
[4] *Ann.*, 1887, **240**, 187.

CHAPTER XII

SEVEN-MEMBERED AND HIGHER RINGS

Introductory:

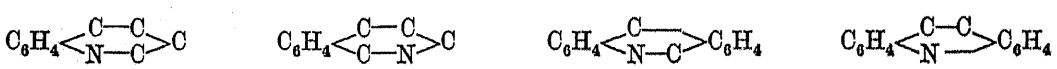
The tendency towards the formation of ring-structures diminishes greatly as the length of a carbon chain increases, and although quite a number of reactions result in the production of derivatives of hexamethyleneimine, very few examples of higher ring compounds are known.

Seven-membered rings have been formed from 1 : 6-diamines (sect. 1), from 1 : 6-amino-halides (sect. 2), from ε-aminoketones of the type

$$NH_2\cdot[CH_2]_5\cdot CO\cdot R$$

(sect. 3) and from ε-amino-acids (sect. 4). In all these cases the ring-closure occurs at the nitrogen atom. Wallach's "*iso*oximes" (sect. 5) from *cyclo*hexanones are seven-membered lactams. Ring-closure between carbon atoms (3) and (4) also leads in two cases to hexamethylene-imine derivatives (sects. 6 and 7).

A variety of syntheses resulting in cyclic compounds of the types

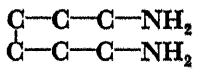


are described in section 8, together with an example of a *meta* ring.

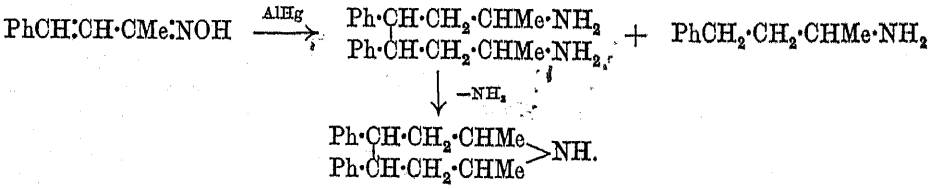
Ring compounds containing eight, ten and eleven members are also known.

HEXAMETHYLENEIMINES

1. From 1:6-diamines:



Bargellini [1] claims to have obtained 2 : 7-dimethyl-4 : 5-diphenylhexamethyleneimine by heating the hydrochloride of a diamine formed during the reduction of benzalacetone oxime:



[1] *R. A. L.*, 1907, [v], **16**, ii, 344.

2. From 1 : 6-amino-halides : $\begin{matrix}C\cdot C\cdot C\cdot X\\ C\cdot C\cdot C\cdot NH_2\end{matrix}$

Hexamethylenimine itself was prepared by v. Braun and Steindorff [1] by the following method:

$$\begin{matrix}CH_2\cdot CH_2\cdot CH_2\cdot OPh\\ CH_2\cdot CH_2\cdot CN\end{matrix} \xrightarrow[Na+alc.]{} \begin{matrix}CH_2\cdot CH_2\cdot CH_2\cdot OPh\\ CH_2\cdot CH_2\cdot CH_2\cdot NH_2\end{matrix} \xrightarrow[80\text{–}90^\circ]{HCl \text{ or } HBr}$$

(83% yield.)

$$\begin{matrix}CH_2\cdot CH_2\cdot CH_2X\\ CH_2\cdot CH_2\cdot CH_2NH_2\end{matrix} \longrightarrow \begin{matrix}CH_2\cdot CH_2\cdot CH_2\\ CH_2\cdot CH_2\cdot CH_2\end{matrix}>NH.$$

(100% yield.)

The yield in the final stage was poor, only 2 gms. being obtained from 20 gms. of phenoxynitrile originally used. The constitution of the product was proved [2] by treating the benzoyl derivative with PCl_5 followed by PhONa; it is thus converted into 1 : 6-diphenoxyhexane.

v. Braun [3] has also attempted to prepare seven-membered ring-compounds by the action of methylamine and of aniline upon 1 : 6-diiodohexane (I), but without success.

$$\begin{matrix}CH_2\cdot CH_2\cdot CH_2I\\ CH_2\cdot CH_2\cdot CH_2I\end{matrix}$$

(I.)

3. From ε-aminoketones : $\begin{matrix}C\cdot C\cdot CO\cdot R\\ C\cdot C\cdot C\cdot NH_2\end{matrix}$

Gabriel found that in the series of ω-aminoketones, $NH_2\cdot[CH_2]_x\cdot CO\cdot R$, cyclisation occurred immediately upon liberation of the base from its salts if $x = 3$ or 4, but where $x = 5$, the free base showed no great tendency to ring-closure.[4] ε-Aminocaprophenone, $NH_2[CH_2]_5\cdot COPh$, gave no ring compound, but the corresponding methyl ketone was cyclised by the action of H_2SO_4 [5]:

$$Br[CH_2]_4\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4 \xrightarrow{CH_3CO\cdot CHNaCOOEt} \begin{matrix}COOEt\\ MeCO\cdot CH\cdot[CH_2]_4\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4\end{matrix} \longrightarrow$$

$$Me\cdot CO\cdot CH_2\cdot[CH_2]_4\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4 \longrightarrow Me\cdot CO\cdot[CH_2]_5\cdot NH_2 \xrightarrow{H_2SO_4} NH<\begin{matrix}CMe:CH\cdot CH_2\\ CH_2\cdot CH_2\cdot CH_2\end{matrix}.$$

An alternative synthesis is from ε-aminocaproic acid (see p. 396):

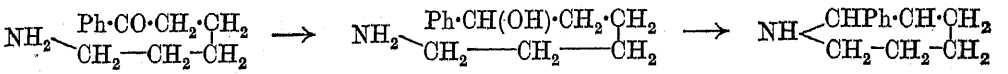
$$PhCO\cdot NH\cdot[CH_2]_5\cdot COOH \xrightarrow{PCl_5} Ph\cdot CO\cdot NH[CH_2]_5\cdot COCl \xrightarrow{NaCH(COOEt)_2}$$

$$Ph\cdot CO\cdot NH\cdot[CH_2]_5\cdot CO\cdot CH(COOEt)_2 \xrightarrow{HCl} NH_2\cdot[CH_2]_5\cdot CO\cdot CH_3 \xrightarrow{H_2SO_4} NH<\begin{matrix}CMe:CH\cdot CH_2\\ CH_2\cdot CH_2\cdot CH_2\end{matrix}.$$

The yield of ε-aminoketone by this method is 23% on the benzoyl-ε-aminocaproic acid.

[1] *Ber.*, 1905, **38**, 3086. [2] v. Braun, *ibid.*, 1910, **43**, 2855. [3] *Ibid.*, p. 2857.
[4] Gabriel and Colman, *ibid.*, 1908, **41**, 2014. [5] Gabriel, *ibid.*, 1909, **42**, 1259.

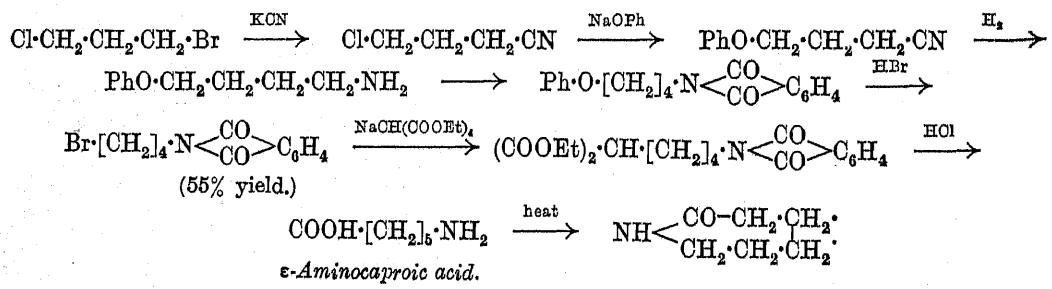
ε-Aminocaprophenone gives a seven-membered ring compound on reduction [1]:



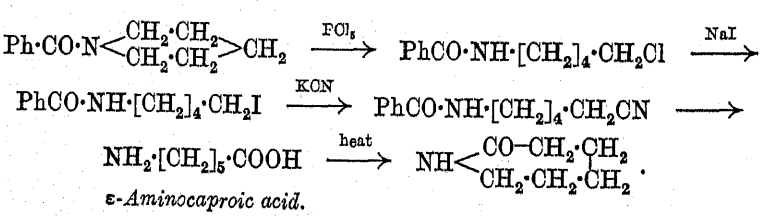
It thus appears either that ε-aminocaprophenone shows no tendency to enolise under the conditions employed, or that the fully saturated C_6N ring is more easily formed than the same ring containing one double bond.

4. From ε-amino-acids: C·C·COOH / C·C·C·NH₂

ε-Aminocaproic acid was synthesised by Gabriel and Maas [2] from γ-phenoxybutyronitrile. It gives a lactam when heated:



The same acid was obtained by v. Braun [3] from benzoylpiperidine. The yield of lactam is only 20–30%, calculated on the acid. It is identical with Wallach's *cyclo*hexanone*iso*oxime (see p. 397):

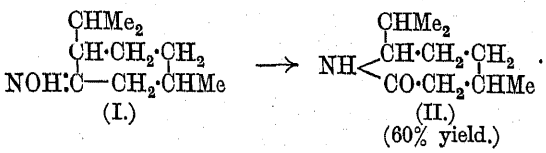


[1] Gabriel, *Ber.*, 1909, **42**, 1267. [2] *Ibid.*, 1899, **32**, 1267. [3] *Ibid.*, 1907, **40**, 1839.

5. From oximes of *cyclo*hexanones etc.: C·C·C / C·C·C:NOH

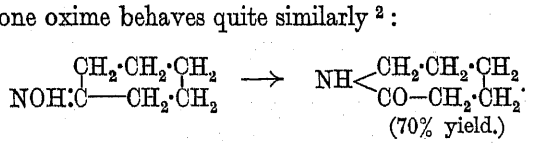
As has already been explained (p. 235) the product of the Beckmann change in the case of the oximes of cyclic ketones is an "*iso*oxime," which is a lactam formed by absorption of ·NH· into the ring.

The first example was the conversion of menthone oxime (I) into its *iso*oxime (II) by means of PCl_5 or, better, conc. H_2SO_4 [1]:



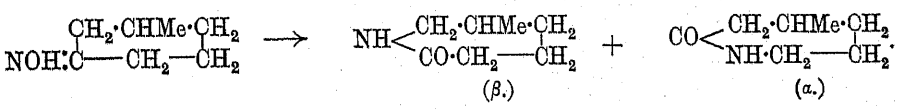
(I.) (II.) (60% yield.)

The simpler *cyclo*hexanone oxime behaves quite similarly [2]:



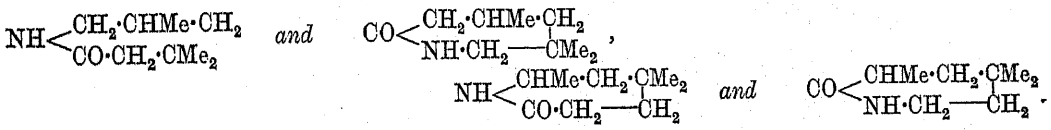
(70% yield.)

From 3-methyl*cyclo*hexanone oxime two isomeric *iso*oximes are produced [3]:



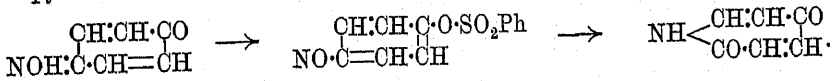
(β.) (α.)

3 : 3 : 5- and 2 : 4 : 4-Trimethyl*cyclo*hexanone oximes also yield pairs of *iso*oximes [4]:



Only one *iso*oxime has been isolated in the case of menthone and of tetrahydrocarvone.[5]

Beckmann and Liesche [6] have extended the reaction to *p*-nitrosophenol. This substance gives only HCl addition products when treated with the Beckmann mixture or with PCl_5, but it can be converted into the *iso*oxime by heating with benzenesulphonyl chloride and pyridine. The benzenesulphonate of nitrosophenol is first formed and this gives the *iso*oxime when further heated with pyridine:



The dioxime of benzoquinone gives no *iso*oxime.

[1] Wallach, *Ann.*, 1893, **277**, 156; 1894, **278**, 304; 1900, **312**, 197.
[2] *Idem, ibid.*, 1900, **312**, 187; 1905, **343**, 43; Ruzicka, *Helv.*, 1921, **4**, 477.
[3] Wallach, *Ann.*, 1899, **309**, 2; 1900, **312**, 191; 1904, **332**, 347; 1906, **346**, 253.
[4] *Idem, ibid.*, 1902, **324**, 107; 1906, **346**, 253.
[5] *Idem, ibid.*, 1900, **312**, 197, 203.
[6] *Ber.*, 1923, **56**, 13.

6. From γ-dibromodipropylamine: $N<^{C-C-CX}_{C-C-CX}$

The Fittig-Wurtz synthesis has been applied by v. Braun to the preparation of *N*-cyano-hexamethyleneimine.[1] The yield is small:

$$Br\cdot[CH_2]_3\cdot OPh + Na_2N\cdot CN \longrightarrow CN\cdot N<^{CH_2\cdot CH_2\cdot CH_2Br}_{CH_2\cdot CH_2\cdot CH_2Br} \quad \textit{and} \quad CN\cdot N<^{CH_2\cdot CH_2\cdot CH_2\cdot OPh}_{CH_2\cdot CH_2\cdot CH_2\cdot OPh}$$

Sodium cyanamide.

$$CN\cdot N<^{CH_2\cdot CH_2\cdot CH_2Br}_{CH_2\cdot CH_2\cdot CH_2Br} \xrightarrow{+Na} CN\cdot N<^{CH_2\cdot CH_2\cdot CH_2}_{CH_2\cdot CH_2\cdot CH_2}.$$

7. From di-[phenacylomethyl]-methylamine: $N<^{C-C-COR}_{C-C-COR}$

The secondary amine (I) obtained by the action of methylamine and formaldehyde upon acetophenone [2] is converted into a cyclic pinacone when reduced with activated aluminium and water:

$$MeNH_2 + CH_2O + 2CH_3COPh \longrightarrow MeN<^{CH_2\cdot CH_2\cdot COPh}_{CH_2\cdot CH_2\cdot COPh} \longrightarrow MeN<^{CH_2\cdot CH_2\cdot CPh(OH)}_{CH_2\cdot CH_2\cdot CPh(OH)}$$

i.e. $MeNH\cdot CH_2(OH)$ (I.)

8. Benzo- and dibenzo-derivatives:

Tetrahydrohomoquinoline was prepared by v. Braun and Bartsch [3] in good yield from *o*-amino-ω-chlorobutylbenzene:

$$C_6H_4<^{CH_2\cdot CH_2\cdot CH_2}_{NH_2 \quad\quad CH_2Cl} \xrightarrow[NaOH]{\text{dilute}} C_6H_4<^{CH_2\cdot CH_2\cdot CH_2}_{NH\text{——}CH_2}.$$

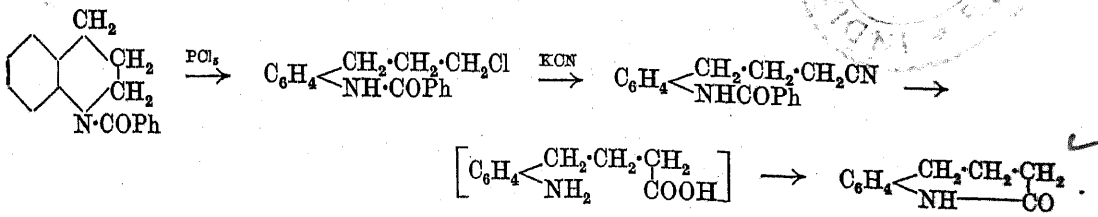
Other methods of obtaining this compound or its isomeride—heating the corresponding diamine hydrochloride (I) or treating ω-aminopropylbenzene (II) with formaldehyde—were completely unsuccessful.

$$C_6H_4<^{CH_2\cdot CH_2\cdot CH_2}_{NH_2 \quad\quad CH_2\cdot NH_2\cdot HCl}$$ (I.)

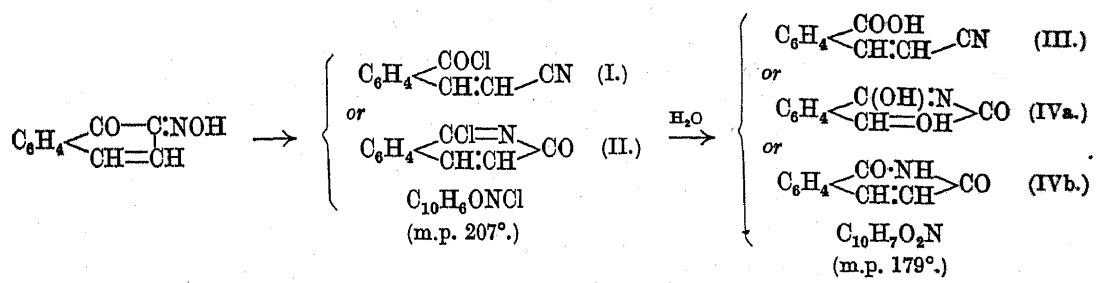
$$C_6H_5\text{—}^{CH_2\cdot CH_2\cdot CH_2}_{(CH_2O) \quad NH_2}$$ (II.)

[1] *Ber.*, 1913, **46**, 1787. [2] Mannich and Heilner, *ibid.*, 1922, **55**, 358, 364.
[3] *Ibid.*, 1912, **45**, 3376; v. Braun and Zobel, *ibid.*, 1923, **56**, 690.

Homohydrocarbostyril is the lactam of *o*-aminophenylbutyric acid. The free acid undergoes ring-closure at once on liberation from its salts [1]:



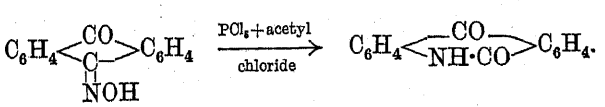
Beckmann and Liesche [2] have studied the conversion of *β*-nitroso-*α*-naphthol into an *iso*-oxime (see p. 397). By the action of PCl_5 in ether, the Beckmann mixture or benzene-sulphonyl chloride and pyridine a compound $C_{10}H_6ONCl$, m. p. 207°, was obtained, the chlorine of which was readily hydrolysed by boiling water to give the substance $C_{10}H_7O_2N$, m. p. 179°:



Borsche and Sander [3] had previously obtained by the action of PCl_5 an isomeric $C_{10}H_6ONCl$, m. p. 83°, to which they gave the structure (I). Beckmann and Liesche suggest for Borsche's compound the formula (II) and for their own the formula (I). These two compounds may, however, be tautomeric forms.

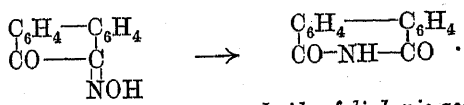
The dioximes of *α*- and *β*-naphthaquinones give no *iso*oximes, nor does 4-nitroso-1-naphthol.

A dibenzo-seven-membered ring was prepared by Beckmann and Liesche [4] from anthraquinone monoxime:



This change is not brought about by the Beckmann mixture, by conc. H_2SO_4 or by benzene-sulphonyl chloride and pyridine.

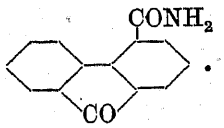
A similar Beckmann change was observed as early as 1889 [5] in the case of phenanthraquinone monoxime:



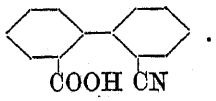
Imide of diphenic acid.

[1] v. Braun, *Ber.*, 1907, **40**, 1841; v. Braun and Rawicz, *ibid.*, 1916, **49**, 806.
[2] *Ibid.*, 1923, **56**, 5.
[3] *Ibid.*, 1914, **47**, 2825.
[4] *Loc. cit.*, p. 16.
[5] Beckmann and Wegerhoff, *Ann.*, 1889, **252**, 14.

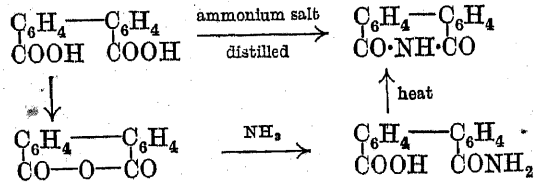
Here the Beckmann mixture succeeds, while conc. H_2SO_4 produces the fluorenone derivative



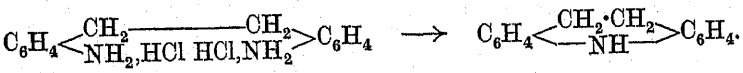
Benzenesulphonyl chloride and pyridine convert phenanthraquinone monoxime into 2-cyano-diphenyl-2′-carboxylic acid [1]



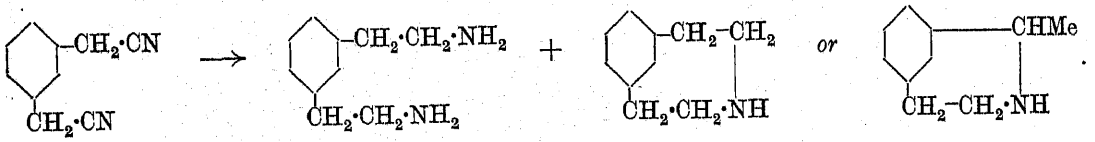
The imide of diphenic acid has also been prepared by Graebe and Aubin [2]:



Thiele and Holzinger [3] prepared "homodihydroacridine" in 60% yield by heating the hydrochloride of the corresponding diamine:

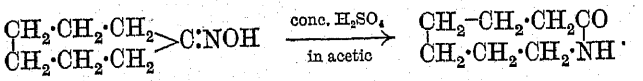


The reduction of *m*-xylylene dicyanide [4] gives only a 5% yield of the diamine, the main product (35% yield) being a seven- or an eight-membered *meta* ring compound:



EIGHT-MEMBERED RINGS, C_7N

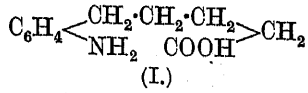
Only two examples of the C_7N ring are at present known. Suberone *iso*oxime was prepared by Wallach [5]:



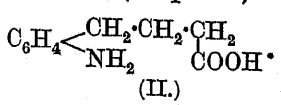
Manasse [6] and v. Braun [7] failed to obtain any trace of this lactam by heating the corresponding acid $NH_2\cdot[CH_2]_6\cdot COOH$.

[1] Werner and Piguet, *Ber.*, 1904, **37**, 4295. [2] *Ann.*, 1888, **247**, 263. [3] *Ibid.*, 1899, **305**, 100.
[4] v. Braun, Karpf and Garn, *Ber.*, 1920, **53**, 103.
[5] *Ann.*, 1899, **309**, 19; 1900, **312**, 205; 1902, **324**, 307. [6] *Ber.*, 1902, **35**, 1367. [7] *Ibid.*, 1907, **40**, 1841.

o-Aminophenylvaleric acid (I) also could not be converted into a lactam,[1] though the lower homologue (II), as already mentioned, exists only in lactam form (see p. 399):

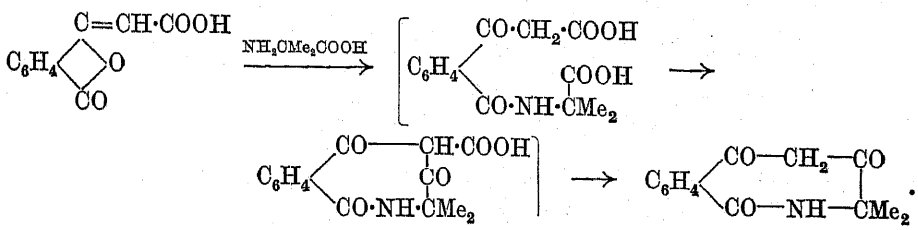


(I.)



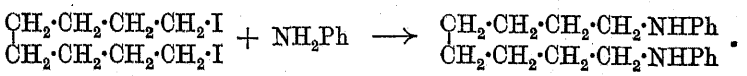
(II.)

Gabriel[2] assigns a C_7N-ring structure to the product obtained from α-amino*iso*butyric acid and phthalideacetic acid:



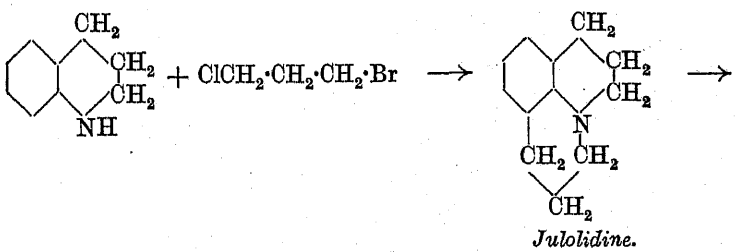
NINE-MEMBERED RINGS, C_8N

All attempts to obtain octomethyleneimine have been unsuccessful. Blaise and Houillon[3] heated the corresponding diamine hydrochloride, but the product was a 2-butylpyrrolidine. v. Braun[4] similarly failed to obtain a 9-ring by heating 1 : 8-di-iodo-octane with aniline:

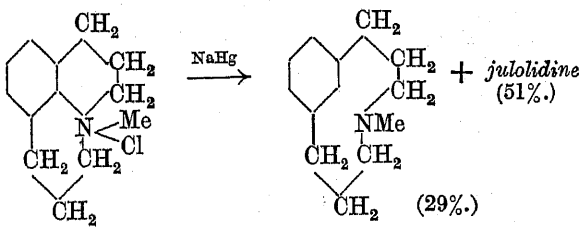


TEN-MEMBERED RINGS, C_9N

A ten-membered ring C_9N has been synthesised by v. Braun and his co-workers[5] by reduction of julolidine methochloride with sodium amalgam:

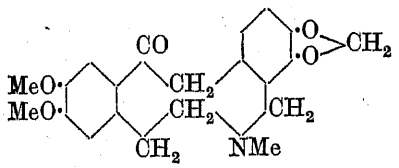


Julolidine.

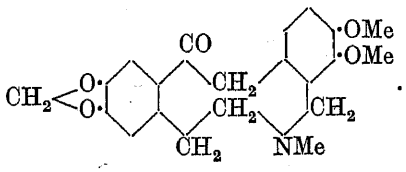


[1] Diels and Einhorn, *Ber.*, 1887, **20**, 377. [2] *Ibid.*, 1911, **44**, 76. [3] *Compt. rend.*, 1906, **142**, 1541.
[4] *Ber.*, 1909, **42**, 4546. [5] *Ibid.*, 1918, **51**, 1225; 1919, **52**, 2015.

A 10-ring structure has been assigned by Perkin to two opium alkaloids, cryptopine and protopine [1]:

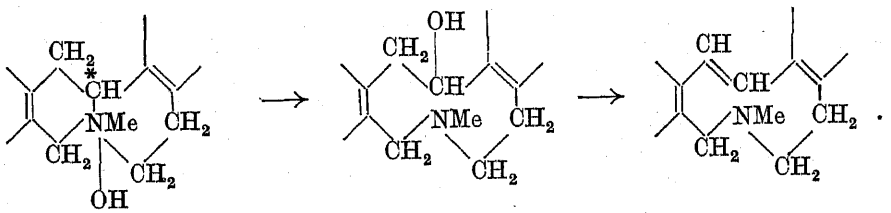


Cryptopine.



Protopine.

The 10-ring also occurs in certain degradation products of tetrahydroberberine (*dl*-canadine). This was first suggested by Voss and Gadamer [2] to explain the formation of an inactive anhydrobase by the action of AgOH upon tetrahydroberberine alkyl iodides:



Since the optical activity depends upon the ·CH· marked with an asterisk, this carbon atom must be involved in the anhydrisation, and to this the ·OH group must wander.

Compounds of this type were obtained by Freund [3] from α-benzyltetrahydroberberine methiodide, and by Pyman [4] from tetrahydroberberine and *l*-canadine meth-hydroxides by evaporation *in vacuo* (54% yield).

ELEVEN-MEMBERED RINGS, $C_{10}N$

Phookan and Krafft [5] synthesised decamethylenediamine from sebacic acid *via* the diamide and dinitrile, and by heating the hydrochloride obtained a product which they considered to be decamethyleneimine. Blaise and Houillon [6] showed, however, that α-hexylpyrrolidine and a mixture of other bases were formed, and none of the products gave ω-aminocaproic acid, $NH_2·[CH_2]_9·COOH$, by benzoylation, oxidation and hydrolysis (as alleged by Phookan and Krafft).

[1] *J. C. S.*, 1916, **109**, 831, 875; 1919, **115**, 713.
[2] *Arch. Pharm.*, 1910, **248**, 43.
[3] *Ann.*, 1913, **397**, 75.
[4] *J. C. S.*, 1913, **103**, 828.
[5] *Ber.*, 1892, **25**, 2252.
[6] *Compt. rend.*, 1906, **143**, 361.

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["+" = *condensation with*; "→" = *conversion into*.]

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